No. 2016-2325

IN THE

United States Court of Appeals for the Federal Circuit

TAKEDA PHARMACEUTICAL COMPANY LIMITED; TAKEDA PHARMACEUTICALS U.S.A., INC.; and TAKEDA PHARMACEUTICALS AMERICA, INC.,

Plaintiffs-Appellants,

v.

SUN PHARMA GLOBAL FZE and SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants-Appellees.

Appeal from the United States District Court for the District of New Jersey
Case No. 3:14-cv-04616, Judge Mary L. Cooper

CORRECTED OPENING BRIEF FOR APPELLANTS

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CERTIFICATE OF INTEREST

Counsel for Plaintiffs-Appellants hereby certifies as follows:

1. The full name of every party represented by me is: Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals U.S.A., Inc., and Takeda Pharmaceuticals America, Inc.

2. The parties named in the caption are the real parties in interest.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of the parties I represent are as follows:

a. Takeda Pharmaceutical Company Limited No company owns 10% or more of the stock of Takeda Pharmaceutical Company Limited.

b. Takeda Pharmaceuticals U.S.A., Inc. Takeda Pharmaceuticals U.S.A., Inc., is a wholly owned subsidiary of Takeda America Holdings, Inc., which is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

c. Takeda Pharmaceuticals America, Inc. Takeda Pharmaceuticals America, Inc., is a wholly owned subsidiary of Takeda Pharmaceuticals U.S.A., Inc., which is a wholly owned subsidiary of Takeda America Holdings, Inc., which is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

4. The names of all law firms and partners or associates that appeared for the parties represented by me in the trial court or that are expected to appear in this court are:

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Dated: September 14, 2016 /s/ Arlene L. Chow

TABLE OF CONTENTS

Page

CERTIFICATE OF INTEREST i

TABLE OF AUTHORITIES v

STATEMENT OF RELATED CASES vii

JURISDICTION 1

INTRODUCTION 2

ISSUE PRESENTED FOR REVIEW 4

STATEMENT OF THE CASE 4

I. BACKGROUND 4

II. PROCEDURAL HISTORY 6

SUMMARY OF THE ARGUMENT 9

ARGUMENT 12

I. STANDARD OF REVIEW 12

II. THE DISTRICT COURT ERRED IN GRAFTING AN EXTRANEOUS LIMITATION ONTO THE "ENTERIC COATING LAYER" CLAIM TERM 13

A. The Plain Meaning of the Claim Term Requires Rejection of the District Court's "Not Chemically the Same" Limitation 15

B. There Was No Lexicography or Disavowal 21

C. Though the District Court Did Not Rely on Extrinsic Evidence, The Extrinsic Evidence Presented to the District Court Supports Takeda's Position 28

TABLE OF CONTENTS – Continued

Page

III. THE CONSTRUCTION PROPOSED BY TAKEDA DIRECTLY TRACKS THE SPECIFICATION AND IS CONSISTENT WITH THE PLAIN AND ORDINARY MEANING OF THE CLAIM TERM 31

CONCLUSION 34

ADDENDUM

CERTIFICATE OF SERVICE

CERTIFICATE OF COMPLIANCE

TABLE OF AUTHORITIES

Page

CASES:

C.R. Bard, Inc. v. U.S. Surgical Corp.,
388 F.3d 858 (Fed. Cir. 2004) 29

Electro Med. Sys. S.A. v. Cooper Life Sciences, Inc.,
34 F.3d 1048 (Fed. Cir. 1994) 14, 24

Hill-Rom Services, Inc. v. Stryker Corp.,
755 F.3d 1367 (Fed. Cir. 2014) 13, 14, 15, 21

Luminara Worldwide, LLC v. Liown Electronics Co.,
814 F.3d 1343 (Fed. Cir. 2016) 15

Omega Eng'g, Inc. v. Raytek Corp.,
334 F.3d 1314 (Fed. Cir. 2003) 22

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed Cir. 2005) (en banc) 13, 14, 28, 29

SanDisk Corp. v. Memorex Products, Inc.,
415 F.3d 1278 (Fed. Cir. 2005) 27

Southwall Technologies, Inc. v. Cardinal IG Co.,
54 F.3d 1570 (Fed. Cir. 1995) 29

Teleflex, Inc. v. Ficosa N. Am. Corp.,
299 F.3d 1313 (Fed. Cir. 2002) 22

Teva Pharm. USA v. Sandoz, Inc.,
135 S. Ct. 831 (2015)....................9, 12

Thorner v. Sony Computer Entm't Am. LLC,
669 F.3d 1362 (Fed. Cir. 2012) 13, 16, 21, 24

STATUTES:

28 U.S.C. § 1295(a)(1)....................1

28 U.S.C. § 1338(a) 1

TABLE OF AUTHORITIES – Continued

Page

28 U.S.C. § 2107 1

RULES:

Fed. R. App. P. 4(a) 1

Local Patent Rule 3.7 8

OTHER AUTHORITIES:

Fuchsia Dunlop, *Every Grain of Rice: Simple Chinese Home Cooking* (W.W. Norton & Co., 2013) 20

Merriam-Webster's Collegiate Dictionary (11th ed. 2005) 18

OED Online (Sept. 12, 2016) 18

STATEMENT OF RELATED CASES

No appeal in or from the same proceeding in the lower court was previously before this Court or any other appellate court. No case known to counsel to be pending in this or any other court will directly affect or be directly affected by this Court's decision in the pending appeal.

IN THE

United States Court of Appeals for the Federal Circuit

TAKEDA PHARMACEUTICAL COMPANY LIMITED, et al.,
Plaintiffs-Appellants,

v.

SUN PHARMA GLOBAL FZE, et al.,
Defendants-Appellees.

Appeal from the United States District Court for the District of New Jersey
Case No. 3:14-cv-04616
Judge Mary L. Cooper

CORRECTED OPENING BRIEF FOR APPELLANTS

JURISDICTION

Takeda[1] appeals from a final judgment of the U.S. District Court for the District of New Jersey, entered on July 6, 2016. Appx1. The District Court had jurisdiction over this patent infringement suit under the Hatch-Waxman Act pursuant to 28 U.S.C. § 1338(a). Takeda filed a timely notice of appeal on July 8, 2016. Appx4214-4216; *see* 28 U.S.C. § 2107; Fed. R. App. P. 4(a). This Court has appellate jurisdiction under 28 U.S.C. § 1295(a)(1). This appeal is from a final order that disposes of all parties' claims.

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[1] "Takeda" refers collectively to Plaintiffs-Appellants Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals U.S.A., Inc., and Takeda Pharmaceuticals America, Inc.

INTRODUCTION

This appeal concerns the construction of a single claim term in U.S. Patent No. 6,328,994 ("the '994 patent"), titled "Orally Disintegrable Tablets." The '994 patent covers Takeda's orally disintegrating tablet ("ODT") formulation of the blockbuster anti-ulcer drug Prevacid®, which is marketed under the brand name Prevacid® SoluTab™. Unlike conventional tablets, the claimed ODT is not meant to be swallowed or chewed; rather, it disintegrates in the patient's mouth without the need for water, leaving behind thousands of tiny enteric-coated granules, which are then swallowed by the patient. (The term "enteric-coated" indicates that the granules are encased so that they pass through the stomach and reach the intestine, where the active ingredient can be safely released.)

Prevacid® SoluTab™ has helped millions of patients with gastrointestinal disorders who have difficulty taking conventional capsules or tablets. Though nine abbreviated new drug applications have been to submitted to FDA, there is currently no generic version on the market. Sun[2] now seeks FDA approval to make and sell its generic lansoprazole ODT product before the expiration of the '994 patent.

The parties dispute the construction of a claim term concerning the "enteric coating layer" of the granules in the claimed tablet: "an enteric coating layer

[2] "Sun" refers collectively to Defendants-Appellees Sun Pharma Global FZE and Sun Pharmaceutical Industries, Ltd.

comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent." Appx66 at 37:46-48. Sun sought to graft three extraneous limitations onto that claim term. The District Court rejected two of these extraneous limitations, but accepted a third: a requirement that the two "component[s]" described in the claim term be made up of different chemical substances. Adopting Sun's proposed language on this point, the District Court construed the claim term as follows: "an enteric coating layer comprising *two discrete components (i.e., not chemically the same)*, namely a first component which is an enteric coating agent and a second component which is a sustained-release agent." Appx12 (emphasis added); Appx20.

In light of the District Court's erroneous construction of this claim term, Takeda stipulated to a judgment of noninfringement and now appeals. The claim term does recite an enteric layer comprising two components, but it does not specify a particular way in which the components must be distinct from one another. Nothing in the claim language, specification, prosecution history, or extrinsic evidence supports the District Court's imposition of a limitation requiring that they be *chemically* distinct. Rather, the ordinary meaning of the claim language aligns with Takeda's proposed construction, which allows for different enteric coating layers with two *physically* distinct components.

ISSUE PRESENTED FOR REVIEW

Whether the District Court erred in construing a claim term that discloses "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent" to require that the two components be "not chemically the same."

STATEMENT OF THE CASE

I. BACKGROUND

An orally disintegrating tablet or "ODT" is a highly desirable formulation that combines the advantages of both liquids and tablets: An ODT provides the convenience of a tablet with the ease of swallowing a liquid. This is especially important for patients who have difficulty swallowing a pill, including children, elderly patients, and persons suffering from GERD (that is, acid reflux), erosive esophagitis, and other acid-related disorders. *See* Appx48 at 2:6-11; Appx56 at 18:1-6. Because ODTs are relatively easy to administer, they improve patient compliance. An ODT also avoids the dangers associated with other tablet and capsule formulations, which can block the esophagus, delaying absorption of the active ingredient or causing ulceration. Appx56 at 18:1-6.

Developing a viable ODT—particularly one containing tiny enteric-coated granules—is not easy. Such ODTs are made up of thousands of tiny granules containing the active ingredient that are combined with tablet ingredients and then compressed to form the tablet. When the tablet is placed in the patient's mouth, the tablet ingredients disintegrate, leaving behind the granules, which are then easily swallowed. Appx2774; Appx2778. Developing and manufacturing ODT formulations can be expensive, technically difficult, and time-consuming, and can require special equipment and special manufacturing conditions. Appx156 at ¶¶ 13-14. This is especially true in the case of lansoprazole, the active ingredient in Prevacid® SoluTab™ and in Sun's generic product, because lansoprazole is acid-labile—that is, it readily breaks down in the presence of acid, such as the gastric acid in the stomach. Appx157 at ¶¶ 16-17. To ensure that the active ingredient passes through the stomach uncompromised and is released in the intestines, acid-labile drugs need to be protected by an enteric coating. *Id*.

Manufacturing ODTs using conventional tableting machines is desirable because such machines are relatively inexpensive and simple to use. Unfortunately, however, the pressure applied by a conventional tableting machine during the compression step used to form the ODT may crack the enteric coating on the granules. *Id*. When the coating cracks, the active ingredient's protection from acid is compromised, leading to the premature release of the drug before it reaches the intestines and raising the risk of degradation, inactivation, and inconsistent dosing. *Id*.

The ’994 patent discloses, *inter alia*, an innovation that addresses the issue of damage to the enteric coat during the tableting process. Specifically, the ’994 patent teaches an enteric coating layer made from a combination of an enteric coating agent, which protects the active ingredient from acid degradation, and a sustained-release agent, which cushions the enteric coating when the granules are compressed into a tablet, thereby increasing the acid-resistance of the formulation. Appx157-158 at ¶¶ 19-23; Appx48-49 at 2:56-3:3; Appx52 at 9:9-26; Appx57 at 19:25-31.

II. PROCEDURAL HISTORY

In response to Sun’s abbreviated new drug application for its generic lansoprazole ODT product, Takeda filed this infringement action in the United States District Court for the District of New Jersey on July 9, 2014. Appx28. Takeda filed a Second Amended Complaint on February 26, 2015. Appx32. The parties proceeded to claim construction on the term “enteric coating layer.” The District Court held a *Markman* hearing on December 2, 2015. The claim language and the parties’ proposed constructions were as follows:

- Claim 1 of the ’994 patent (disputed term in italics): “An orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 µm or less, which fine granules comprise a composition coated by *an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent*, said composition having 10 weight % or more of an acid-labile physiologically active substrate[3] that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to 20 kg, is orally disintegrable." Appx66 at 37:43-53.

- Takeda's proposed construction: "The 'enteric coating layer' may be constructed by plural (*e.g.*, 2 or 3) layers and includes a first component that is an 'enteric coating agent' which can be a methacrylate copolymer and a second component that is a 'sustained-release agent' which can be a methacrylate copolymer." Appx123.

- Sun's proposed construction: "an enteric coating layer comprising two discrete components (i.e., not chemically the same) in an admixture, namely a first component which is an enteric coating agent and a second component which is a sustained-release agent. Eudragit L30D-55 is not a sustained-release agent." *Id*.

The District Court ruled from the bench at the *Markman* hearing, and did not issue a written opinion. The Court rejected two of Sun's proposed additions to the claim language. First, the Court declined "to make a ruling at this claim construction stage whether L30D-55 is a sustained release agent." Appx15. That was an infringement issue, not a claim construction issue. Appx16. Second, the Court rejected Sun's contention that the two components had to be "in an admixture," finding that "the patent is silent, and I'm not going to read that kind of requirement in as a matter of claim construction." Appx20.

But the Court agreed with Sun that the two components of the enteric coating layer had to be chemically distinct. In particular, the Court found that it was "clear" from the prosecution history "that th[e] two-component aspect was

[3] The USPTO has issued a Certificate of Correction acknowledging that the claim should read "substance" rather than "substrate."

material to the examiner's approval of the patent over the objections about the enteric coating layer being old prior art." Appx18. And it decided that "you just simply have to have two *ingredients* in order to be able to be able to practice this invention." Appx18-19 (emphasis added). And for two components to constitute two "ingredients" they had to be "chemically distinguishable." *Id*.

The District Court entered an order setting out its construction of the claim term on December 4, 2015. Appx11-12. Its final construction was: "an enteric coating layer comprising two discrete components (i.e., not chemically the same), namely a first component which is an enteric coating agent and a second component which is a sustained-release agent." *Id*.

Takeda sought leave to amend its infringement contentions in light of the claim construction ruling under Local Patent Rule 3.7, which provides that "[a]mendment of any contentions . . . may be made" upon a "showing of good cause." The Rule specifies that one circumstance supporting a finding of good cause is "a claim construction by the Court different from that proposed by the party seeking amendment." Loc. P. R. 3.7. But the magistrate judge denied Takeda's request, and the District Court affirmed. Appx4213.

In light of the District Court's decision on claim construction, Takeda agreed to the entry of a judgment of noninfringement. The District Court signed the parties' stipulation on June 9, 2016, Appx2-10, and entered its final judgment in favor of Sun in accordance with the stipulation on July 6, 2016, Appx1. Takeda filed its notice of appeal on July 8, 2016. Appx4214-4216.

SUMMARY OF THE ARGUMENT

1. The District Court based its claim construction ruling solely on the intrinsic evidence. Therefore, this Court reviews the ruling de novo. *Teva Pharm. USA v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015).

2. The sole disputed claim term discloses "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent." Appx66 at 37:46-48. Adopting Sun's proposed construction in part, the District Court interpreted the claim term to be limited to "an enteric coating layer comprising two discrete components (i.e., not chemically the same)." Appx12; Appx20. That interpretation introduces an atextual limitation requiring that the two components described in the claim term be "not chemically the same." There is no basis for such a limitation in the claim language, the specification, the prosecution history, or the extrinsic evidence.

No one disputes that the claim term requires two components. But there are many ways for two components to be distinct, and the intrinsic evidence provides no support for the District Court's requirement that they be *chemically* distinct. For instance, two components that occupy different locations would be *physically* distinct and would thus satisfy the requirement of two distinct components even if they were made of the same chemical substance.

The claim term's reference to two agents does not support the District Court's "not chemically the same" limitation. The term "agent" suggests a functional definition, not a specific chemical. For instance, a phrase like "clotting agent" does not point to a particular chemical substance, but rather encompasses every chemical that is suitable for performing the specified function—here, causing blood to coagulate. The claim term's references to an "enteric coating agent" and a "sustained-release agent" are similarly functional. And there is no reason that a single chemical cannot perform multiple different functions—and therefore be different types of agent—depending on context. In the pharmaceutical art, it is both common and well-known that a single pharmaceutical excipient can perform multiple functions. For example, the "authoritative treatise" that Sun relied on in the District Court describes the chemical substance shellac as suitable for use as either an enteric coating agent or a sustained-release agent. Thus, an enteric coating layer comprising two components that are physically distinct but chemically the same would fall within the plain language of the claim term, as long as the chemical in question can function as both an enteric coating agent and a sustained-release agent.

The specification and prosecution history of the ’994 patent do not support a departure from the plain meaning of the claim term. In neither the specification nor the prosecution history does the patentee express an intention to act as lexicographer by redefining terms or to disavow any part of the scope encompassed by the language of the claims. In particular, nothing in the specification makes clear that the claimed invention excludes a composition in which the enteric coating agent is chemically the same as the sustained-release agent. Indeed, the specification says explicitly that the enteric coating agent and sustained-release agent can both be “methacrylate copolymers.” *See* Appx52 at 9:9-29. And the examples and the lists of exemplary chemicals in the specification are plainly illustrative only, so it is improper to read limitations from the specification into the claims.

Finally, the prosecution history shines no new light on the meaning of the claim term; it suggests that the examiner considered it important for the claim term to disclose an enteric coating layer comprising two distinct *components*, but it provides no support for the District Court’s requirement that they be *chemically* distinct. Indeed, Sun conceded below that there is no disavowal in the intrinsic record requiring the enteric coating agent and sustained-release agent to be “not chemically the same.”

3. This Court should adopt Takeda's proposed construction of the disputed claim term: "The 'enteric coating layer' may be constructed by plural (e.g., 2 or 3) layers and includes a first component that is an 'enteric coating agent' which can be a methacrylate copolymer and a second component that is a 'sustained-release agent' which can be a methacrylate copolymer." Takeda's construction acknowledges that the enteric coating layer comprises two distinct components while jettisoning the District Court's unfounded requirement that they be chemically distinct; rather, it allows the two components to be physically distinct, such as in different physical layers coating the claimed granules. As Sun concedes, the specification contemplates a multi-part enteric coating layer. The specification and dependent claims 39 and 40 also clearly indicate that both the enteric coating agent and the sustained-release agent can be a methacrylate copolymer.

ARGUMENT

I. STANDARD OF REVIEW

Because the District Court relied solely on intrinsic evidence in construing the disputed claim term, this Court's review is de novo. *Teva Pharm. USA*, 135 S. Ct. at 841 ("[W]hen the district court reviews only evidence intrinsic to the patent (the patent claims and specifications, along with the patent's prosecution history), the judge's determination will amount solely to a determination of law, and the

Court of Appeals will review that construction de novo." (citations omitted)); *see* Appx21 ("I have made this ruling on the basis of the intrinsic evidence. . . . I find that the intrinsic evidence, as generally informed by the tutorial that these experts have given me, is sufficient for me to understand the limited claim construction issues that I'm ruling on . . . .").

II. THE DISTRICT COURT ERRED IN GRAFTING AN EXTRANEOUS LIMITATION ONTO THE "ENTERIC COATING LAYER" CLAIM TERM.

The patent's claims define the patented invention and thus the scope of the patentee's right to exclude. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed Cir. 2005) (en banc). "Claim terms are generally given their plain and ordinary meanings to one of skill in the art when read in the context of the specification and prosecution history." *Hill-Rom Services, Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014), *cert. denied*, *Stryker Corp. v. Hill-Rom Services, Inc.*, 135 S. Ct. 719 (2014). "There are only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, and 2) when the patentee disavows the full scope of the claim term either in the specification or during prosecution." *Id.* (quoting *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012)).

While claims are read in view of the specification, of which they are part, it is improper to read limitations from the embodiments in the specification into the claims. *Id.*; *see also Electro Med. Sys. S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1054 (Fed. Cir. 1994) ("claims are not to be interpreted by adding limitations appearing only in the specification" (citation omitted)). Moreover, because a patent's prosecution history "represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Phillips*, 415 F.3d at 1317 (citations omitted).

The District Court's oral decision in this case is at odds with these basic principles of claim construction. There is one disputed claim term here, which appears in the '994 patent's two independent claims, claims 1 and 29. Claim 1 recites the following (with the disputed claim term in italics):

> 1. An orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 µm or less, which fine granules comprise a composition coated by *an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent*, said composition having 10 weight % or more of an acid-labile physiologically active [substance] that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to 20 kg, is orally disintegrable.

Appx66 at 37:43-53.

The District Court accepted Sun's proposal to graft onto the "enteric coating layer" claim term a requirement that the two components described be chemically distinct substances. Adopting Sun's proposed language, the District Court construed the disputed claim term as follows: "an enteric coating layer comprising two discrete components (i.e., not chemically the same), namely a first component which is an enteric coating agent and a second component which is a sustained-release agent." Appx12; Appx20. The District Court's construction is wrong. It narrows the plain and ordinary meaning of the claim term by adding an extraneous limitation—the requirement that the two discrete components be *chemically* distinct—that has no basis in the claim language, the specification, the prosecution history, or the extrinsic evidence. This Court should reject the "not chemically the same" limitation.

A. The Plain Meaning of the Claim Term Requires Rejection of the District Court's "Not Chemically the Same" Limitation.

"Absent lexicography or disavowal, we do not depart from the plain meaning of the claims." *Luminara Worldwide, LLC v. Liown Electronics Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016) (citation omitted); *see also Hill-Rom Services, Inc.*, 755 F.3d at 1371. The plain meaning of the disputed claim term is clear: The enteric coating layer must have two components, but those components do not have to be *chemically* distinct.

1. Takeda readily acknowledges that the ordinary meaning of the claim term requires two components; that meaning is conveyed by the claim term's disclosure of "a first component" and "a second component." Therefore, the description in the District Court's construction of "an enteric coating layer comprising two discrete components" is unnecessary but unobjectionable.

However, two components may be distinct in many ways. And nothing in the language of the claim term indicates *how* the two components must be distinct, much less specifies that they must be *chemically* distinct. Rather, the plain and ordinary meaning of the claim language encompasses any composition that has two distinct components where one component is an enteric coating agent and the other component is a sustained-release agent. "It is the claims that define the metes and bounds of the patentee's invention. . . . The patentee is free to choose a broad term and expect to obtain the full scope of its plain and ordinary meaning unless the patentee explicitly redefines the term or disavows its full scope." *Thorner*, 669 F.3d at 1367 (citation omitted). It was therefore inappropriate for the District Court to graft the "not chemically the same" limitation onto the claim term.

The District Court's construction is implausible on its face: The phrase "two discrete components (i.e., not chemically the same)" suggests, through its use of the abbreviation "i.e.," that the requirement of chemical distinctness is simply another way of phrasing the requirement of discreteness. But again, chemical distinctness is just one form of distinctness among many others, and two components that are chemically the same can nonetheless be discrete. The District Court thus erred in conflating "not chemically the same" with the broader concept of discreteness. For instance, two chemically identical components may be physically distinct—that is, they may be discrete components because they occupy separate, distinguishable positions in space. The claim language does not exclude that form of distinctness.

2. In issuing its "not chemically the same" construction, the District Court stated that "you just simply have to have two ingredients in order to be able to practice this invention; two ingredients in the enteric coating layer as defined in the claim language, Claim 1 and 29." Appx18-19. But the '994 patent does not call for two *ingredients*. Rather, the claim term discloses an "enteric coating layer" comprising two distinct *components*, where the "first component . . . is an enteric coating agent" and the "second component . . . is a sustained-release agent." And two "components" can be *physically* distinct even if they are chemically identical. Indeed, the District Court's cooking metaphor is even wrong on its own terms: As explored more fully below, a single chemical "ingredient"—like flour or cornstarch—may perform multiple functions depending on context, and therefore constitute two separate and distinguishable "components" of a finished dish.[4]

The claim term's reference to "an enteric coating agent" and "a sustained-release agent" does not support the District Court's "not chemically the same" limitation; nothing in the language excludes a composition in which a single chemical plays both roles. Indeed, the two components are defined by reference to their *function*, not to any particular chemical substance or substances. This follows from the ordinary meaning of the term "agent" in the context of chemistry and related fields. The term "agent" implies a functional definition, a reference to any of a set of chemical substances that are suitable for use to perform the stated function, and not to a single specific chemical. *See, e.g.*, Merriam-Webster's Collegiate Dictionary (11th ed. 2005) (defining "agent" to mean "something that produces or is capable of producing an effect"); *see also* OED Online (Sept. 12, 2016) (defining "agent" in the context of chemistry to mean a "substance that brings about a chemical or physical effect"). For instance, a reference to "a clotting agent" does not indicate a particular chemical but rather encompasses *any* chemical that is suitable for use to perform the function of causing blood to coagulate.

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[4] The District Court also suggested that, "in order to be able to tell that [a composition] has two discrete components . . . , they at least have to be chemically distinguishable." Appx18. That is simply untrue. One can easily "tell" that two components are "discrete" if they are physically separate.

A single chemical may be able to serve as several types of agent depending on the context in which it is used, since of course a given chemical may be able to perform a multitude of functions in different contexts. If a composition that otherwise falls within the disputed claim includes two physically distinct components such that a single chemical serves as an enteric coating agent in the context of one layer and as a sustained-release agent in the context of another layer, then the composition infringes the '994 patent.

3. A culinary illustration may be helpful. In the abstract, cornstarch is a single ingredient that can act as both a thickening agent and a coating agent: It can be added to sauces and gravies to thicken them, lending them weight and texture, and it can be used along with egg and other ingredients to coat meat or another solid food in preparation for frying.[5] In a given specific context, however, cornstarch may be clearly serving one or the other of these functions. For instance, a dish that includes a sauce thickened by cornstarch would be said to contain cornstarch as a thickening agent; if there is no other cornstarch in the dish, then it would be unnatural to say that the dish contains a coating agent, even though cornstarch is a coating agent *in the abstract*. At the same time, it is of course possible for a particular dish to contain both a thickening agent and a coating agent, and for cornstarch—a single chemical substance or ingredient —to play both of these roles as separate components of the dish.

Thus, the classic American Chinese food recipe for General Tso's chicken comprises a first component that is a coating agent and a second component that is a thickening agent. The coating agent is applied to chunks of raw chicken along with soy sauce and egg yolk, and these coated chunks are then deep-fried. The thickening agent is mixed into a sauce made up of more soy sauce, vinegar, and other ingredients. At the end of the cooking process, the thickened sauce and the coated, deep-fried chicken are mixed together. The coating agent and the thickening agent perform different functions and are clearly distinct in the final product; the coating agent imparts a crisp crust to the chicken as a result of the deep-frying process, and the thickening agent gives the sauce texture and causes it to cling to the chicken. Yet the coating agent and the thickening agent need not be *chemically* distinct. Indeed, a single chemical substance—or ingredient—is most often used to perform both functions; cornstarch is a common choice as both a coating agent and a thickening agent.[6]

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[5] Cornstarch is also used as an anti-caking agent in powdered sugar and baby powder, as an anti-stick agent in medical products made of natural latex (such as medical gloves), and to perform a range of other functions both inside and outside the kitchen.

The lesson is this: Even where a single chemical, such as cornstarch, is used for both functions, the two components are clearly distinct in the final product. And so it is not inconsistent or paradoxical—indeed, it is a natural use of the English language—to say that a dish comprises two distinct components, a coating agent and a thickening agent, even if both agents are formed from the same chemical.

Thus, the plain meaning of the term does not require chemically distinct components; it encompasses a composition in which a single chemical serves both as an "enteric coating agent," which protects the active ingredient from breaking down in stomach acid and thereby allows it to travel safely into the intestine for absorption, and as a "sustained-release agent," by cushioning the granules and thereby protecting them from cracking when compressed into the tablet. The District Court erred in grafting the "not chemically the same" limitation onto the claim term.

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[6] *See, e.g.*, Fuchsia Dunlop, *Every Grain of Rice: Simple Chinese Home Cooking* 122-23 (W.W. Norton & Co., 2013) (recipe for General Tso's chicken).

B. There Was No Lexicography or Disavowal.

Courts "depart from the plain and ordinary meaning of claim terms based on the specification in only two instances: lexicography and disavowal." *Hill-Rom Services, Inc.*, 755 F.3d at 1371 (citation omitted). In this case, there was no lexicography or disavowal to support the District Court's departure from the plain and ordinary meaning of the claim terms as discussed above.

1. "The standards for finding lexicography and disavowal are exacting." *Id.* "'To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning' and must 'clearly express an intent to redefine the term.'" *Id.* (quoting *Thorner*, 669 F.3d at 1365). "Disavowal requires that the specification or prosecution history make clear that the invention does not include a particular feature . . . or is clearly limited to a particular form of the invention." *Id.* at 1372 (internal quotation marks, brackets, and citation omitted); *see also Thorner*, 669 F.3d at 1366 ("The patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or

restriction, representing a clear disavowal of claim scope.") (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002)); *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325-26 (Fed. Cir. 2003) ("[F]or prosecution disclaimer to attach, our precedent requires that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable.").

2. The specification contains no lexicography or disavowal that supports grafting a "not chemically the same" limitation onto the disputed claim term. The standard for lexicography is not met because nothing in the specification "clearly sets forth a definition" or "clearly expresses intent to redefine" the disputed claim term to limit it to components that are chemically distinct. The high standard for disavowal is not satisfied, either: Nothing in the specification "make[s] clear" that the claimed invention excludes a composition in which the enteric coating agent is chemically the same as the sustained-release agent. Indeed, the specification says explicitly that the enteric coating agent and sustained-release agent can both be "methacrylate copolymers." *See* Appx52 at 9:9-29. Even Sun conceded below that there is no disavowal in the intrinsic record requiring the enteric coating agent and the sustained-release agent to be "not chemically the same." *See* Defs.' Mem. in Resp. to Pls.' Opening Claim Construction Br. at 38 (Appx2317) ("Although Plaintiffs may not have explicitly and unambiguously stated within the intrinsic

record that the two claimed components must be different chemical polymers, the intrinsic record and plain and ordinary meaning compel such construction.”).

The specification of the ’994 patent refers to several chemicals that are exemplary enteric coating agents and to several chemicals that are exemplary sustained-release agents. Appx52 at 9:12-13. The specification also discloses nine examples of compositions that practice the claimed invention. Appx57-66. In the District Court, Sun argued that the lack of overlap between the two lists of chemicals and the fact that each of the examples uses two distinct chemicals support an inference that no single chemical could serve as both an enteric coating agent and a sustained-release agent within the meaning of the disputed claim term. But the District Court pointedly refused to rely on the examples in construing the claim term, saying, “I do recognize that each one of the examples in the patent has chemically distinguishable ingredients when it comes to the enteric coating layer, but I’m not basing my ruling about that on the fact that these nine examples have two ingredients.” Appx18.

The District Court was right to reject Sun’s argument. First, the specification’s disclosure of exemplary chemicals and its examples are wholly consistent with the plain import of the claim language that the two components need not be chemically distinct. The lists of chemicals are riddled with terms that make clear that they are merely exemplary rather than exhaustive, including “for example," "such as," "e.g.," and "etc." Appx52 at 9:11-23. And the examples are just that: non-exhaustive illustrations. Even if the specification were less clear on this point, it is well-settled law that it is improper to import limitations from the examples into the claim. *See Thorner*, 669 F.3d at 1366-67 ("It is likewise not enough that the only embodiments, or all of the embodiments, contain a particular limitation. We do not read limitations from the specification into claims; we do not redefine words. Only the patentee can do that. To constitute disclaimer, there must be a clear and unmistakable disclaimer."); *Electro Med. Sys. S.A.*, 34 F.3d at 1054 ("[A]lthough the specifications may well indicate that certain embodiments are preferred, particular embodiments appearing in a specification will not be read into the claims when the claim language is broader than such embodiments." (citation omitted)). Finally, as discussed below, there *are* chemicals well known in the art that can function as both enteric coating agents and sustained-release agents; shellac is one such chemical. In short, nothing in the specification warrants reading a "not chemically the same" limitation into the disputed claim term.

3. The prosecution history of the '994 patent also does not support a departure from the plain and ordinary meaning of the claim term. The District Court relied heavily on the prosecution history in construing the claim term to require chemically distinct components. *See* Appx16-19. In particular, the District Court's decision rested on two elements of the prosecution history: (1) the fact that

the application was rejected when the claim disclosed an "enteric coating layer" without further limitation but approved after it was redrafted to disclose "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent,"[7] and (2) the examiner's statement upon allowance that "[t]he cited prior art does not fairly teach or suggest an oral composition comprising a first component which is an enteric coating and a second component which is a sustained-release agent." Appx16-18. The District Court thus concluded:

> So, it is very clear that this two-component aspect was material to the examiner's approval of the patent over the objections about the enteric coating layer being old prior art.
>
> If you look carefully at that sentence you can see the examiner didn't say it exactly right, but he had the concept, basically. And, so, I find that you can't tell whether an accused composition infringes the patent unless you can tell that it has two discrete components. And in order to be able to tell that it has two discrete components within the language and specification and prosecution history, they at least have to be chemically distinguishable.

Appx18.

In fact, as is apparent even from the District Court's own discussion, the prosecution history lends no support to the "not chemically the same" limitation. It does not add anything to the plain and ordinary meaning of the claim term at issue.

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[7] In an intermediate step of the prosecution history, the claim was amended to disclose "an enteric coating layer comprising a sustained-release agent." After the examiner maintained the original rejection of the claim, the claim was amended a second time to the final language now at issue, and the patent was then allowed.

Yes, the prosecution history suggests that the inclusion of the disputed claim term was relevant to the examiner's decision to allow the patent. But that fact alone provides no insight as to *how* the claim should be construed, and certainly does not suggest that the claim term should be construed to include an unwritten "not chemically the same" limitation.

As the District Court indicated, the examiner was apparently concerned by the term "enteric coating layer," because, in his view, such an enteric coating layer was already present in a piece of prior art, European Patent 761212 A2. Appx16-17. After the claim term was redrafted to disclose "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent," however, the examiner was satisfied and allowed the patent on the ground that "[t]he cited prior art does not fairly teach or suggest an oral composition comprising a first component which is an enteric coating and a second component which is a sustained-release agent." Appx940. The examiner's language closely tracks the disputed claim term and adds nothing to the analysis of whether that term should be construed to include a "not chemically the same" limitation. It does suggest that it was relevant to the examiner's allowance of the patent that the claim term recites two distinct *components*, but, as discussed above, that does not mean that the components must be chemically distinct—they could be distinct even if chemically the same (for instance, if they are physically distinct). Because the prosecution history "is subject to more than one reasonable interpretation, one of which is consistent with a proffered meaning of the disputed term," there is "no 'clear and unmistakable' disclaimer." *SanDisk Corp. v. Memorex Products, Inc.*, 415 F.3d 1278, 1287 (Fed. Cir. 2005) (citation omitted).

To return to our culinary illustration, a recipe for General Tso's chicken that discloses both a coating agent and a thickening agent would represent an advance over, and would be distinct from, an earlier recipe that discloses only a coating agent. This is true even though the newer recipe could be practiced with a single substance, such as cornstarch, acting as both the coating agent (to coat the chicken prior to frying) and the thickening agent (to thicken the sauce). Although the earlier recipe discloses a dish with a coating agent and cornstarch can serve as a coating agent as well as a thickening agent, it would be wrong as a matter of English to say that the earlier recipe discloses a dish with a thickening agent or that the inventor of the newer recipe has therefore disavowed from the scope of her recipe a dish that uses cornstarch (or any other single substance) for both roles.

The intrinsic evidence provides no support for the District Court's additional claim term. In light of the foregoing, a person of ordinary skill in the art would not understand the claim term to include a silent "not chemically the same" limitation. The District Court erred in grafting that extraneous limitation onto the claim.

C. Though the District Court Did Not Rely on Extrinsic Evidence, The Extrinsic Evidence Presented to the District Court Supports Takeda's Position.

The plain and ordinary meaning of the disputed claim term allows for a single chemical to serve as both "a first component which is an enteric coating agent and a second component which is a sustained-release agent" so long as the two required components are distinct in some way (for instance, physically distinct in plural layers). As explained above, all the intrinsic evidence aligns with this plain meaning. In the District Court, Sun contended that the claim term cannot mean what it seems to mean because a person of ordinary skill in the art would understand that no chemical exists that is suitable (in the appropriate context) for use as either an enteric coating agent or a sustained-release agent. *See* Appx516 ("Enteric agents and sustained-release agents refer to different types of polymers."); Appx533 ("an enteric agent . . . by definition is different than a sustained-release agent"). In fact, the extrinsic evidence undermines Sun's claim construction position.

This Court has "viewed extrinsic evidence in general as less reliable than the patent and its prosecution history in determining how to read claim terms, for several reasons." *Phillips*, 415 F.3d at 1318. For one, "extrinsic evidence consisting of expert reports and testimony is generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Moreover, "there is a virtually unbounded universe of potential extrinsic evidence of some marginal relevance that could be brought to bear on any claim construction question. In the course of litigation, each party will naturally choose the pieces of extrinsic evidence most favorable to its cause, leaving the court with the considerable task of filtering the useful extrinsic evidence from the fluff." *Id.* (citation omitted). "Finally, undue reliance on extrinsic evidence poses the risk that it will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history,' thereby undermining the public notice function of patents." *Id.* at 1318-19 (quoting *Southwall Technologies, Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1578 (Fed. Cir. 1995)). Thus, "while extrinsic evidence can shed useful light on the relevant art, . . . it is less significant than the intrinsic record in determining the legally operative meaning of claim language." *Id.* at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)) (internal quotation marks omitted).

Nothing in the extrinsic evidence submitted by the parties justifies departure from the plain and ordinary meaning of the disputed claim term or supports the adoption of the "not chemically the same" limitation. To the contrary, such a limitation runs against the understanding of a person of ordinary skill in the art. It is well known in the pharmaceutical art that pharmaceutical excipients (inactive substances) often have multiple functions depending on the context in which they are used. And there are numerous excipients that function as both enteric coating agents and as sustained-release agents.

For example, the resin shellac is known in the art as a substance that is suitable to act as either an enteric coating agent or a sustained-release agent. In the District Court, Sun relied on what it described as "[a] well-known reference by Lieberman et al." Appx539; *see also* Appx2293 (Lieberman is an "authoritative reference"); Appx2309 n.13 (Lieberman is an "authoritative treatise[]"). Lieberman discloses shellac as both an enteric coating agent and a sustained-release agent. *Compare* Appx726 (disclosing shellac as a polymer used in enteric film coatings), *with* Appx727 (disclosing shellac as a polymer used in sustained-release film coatings); *see also* Appx2143 at 176:18-23 ("[I]n the Lieberman reference, they list shellac under the enteric coating agent and extended release agent, so it is apparent that there is overlap since the coatings made by shellac would form both categories."); Appx52 at 9:11-20 (disclosing shellac as an example of an aqueous enteric polymer agent). Thus, Sun's own "well-known" reference demonstrates that a particular excipient can indeed perform different functions in different contexts and thereby serve as multiple types of agent, and, moreover, that a particular excipient can serve as either an enteric coating agent or a sustained-release agent. And under the plain meaning of the disputed claim term, a composition that used shellac as both an enteric coating agent and a sustained-release agent in discrete layers would, if it met the other limitations, practice the patented invention.

III. THE CONSTRUCTION PROPOSED BY TAKEDA DIRECTLY TRACKS THE SPECIFICATION AND IS CONSISTENT WITH THE PLAIN AND ORDINARY MEANING OF THE CLAIM TERM.

In the District Court, Takeda proposed the following construction of the disputed claim term: "The 'enteric coating layer' may be constructed by plural (e.g., 2 or 3) layers and includes a first component that is an 'enteric coating agent' which can be a methacrylate copolymer and a second component that is a 'sustained-release agent' which can be a methacrylate copolymer." Appx123. Takeda's construction directly tracks the specification and is consistent with the plain and ordinary meaning of the term as understood by a person of skill in the art in view of the intrinsic evidence.

1. The statement that the enteric coating layer "may be constructed by plural (e.g., 2 or 3) layers" accords with the intrinsic evidence. As discussed above, the claim requires that the enteric coating layer comprise two components, and that requirement would be satisfied if the components were physically distinct. For instance, two components would be physically distinct if they occupied separate, distinguishable layers, like the layers of an onion.

And the specification of the ’994 patent contemplates an enteric coating layer that is itself made up of several distinct smaller layers. The specification clearly states that “[t]he ‘enteric coating layer’ may be constructed by plural (e.g., 2 or 3) layers.” Appx55 at 16:37-38. Examples 5, 6, 7, and 8 in the patent specification all comprise “plural . . . layers.” Appx60-65; *see also* Appx547 (acknowledgment by Sun that “the ’994 patent discloses the potential for multiple enteric layers”). The specification thus confirms that the “enteric coating layer” disclosed by the claim term need not be indivisible and can itself comprise plural smaller layers.

2. The intrinsic evidence also supports the second half of Takeda’s proposed construction, which states that “[t]he ‘enteric coating layer’ . . . includes a first component that is an ‘enteric coating agent’ which can be a methacrylate copolymer and a second component that is a ‘sustained-release agent’ which can be a methacrylate copolymer.” The only thing that the proposed construction adds to the language of the claim term is the point that the enteric coating agent and the sustained-release agent “can be a methacrylate copolymer.” Sun conceded that point below, stating that “certain methacrylate copolymers are enteric, while others are sustained-release.” Appx2311; *see also* Appx527 (“There is no doubt that a sustained-release agent ‘*can* be a methacrylate copolymer’”).

The specification of the ’994 patent is clear on this point as well. It states that:

> The above “enteric coating layer” . . . includes, for example, an aqueous enteric polymer agent *such as* . . . *methacrylate copolymer* . . . [and] a sustained-release agent *such as methacrylate copolymer* . . . . The “aqueous enteric polymer agent” is preferably *a methacrylate copolymer*. The sustained-release agent is preferably *a methacrylate copolymer*.

Appx52 at 9: 9-29 (emphases added). This is echoed in the ’994 patent’s claims: Dependent claim 39 specifies that the aqueous enteric polymer agent is a methacrylate copolymer, and dependent claim 40 specifies that the sustained-release agent is a methacrylate copolymer. Appx67 at 40:1-4. Extrinsic evidence likewise defines methacrylate copolymers as being enteric coating agents and sustained-release agents. Appx161 at ¶ 32.

Finally, there is nothing anomalous about specifying that the enteric coating agent and the sustained-release agent can each be a methacrylate copolymer. As discussed above, the two components do not need to be chemically distinct. Takeda’s proposed construction is analogous to the perfectly reasonable (if unwieldy) statement that “General Tso’s chicken includes a first component that is a ‘coating agent’ which can be cornstarch and a second component that is a ‘thickening agent’ which can be cornstarch.”

This Court should therefore adopt Takeda’s proposed claim construction.

CONCLUSION

For the foregoing reasons, the District Court's judgment of noninfringement should be reversed, and the case should be remanded for further proceedings.

Respectfully submitted,

/s/ Arlene L. Chow

September 14, 2016

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ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED, TAKEDA PHARMACEUTICALS U.S.A., INC., and TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. SUN PHARMA GLOBAL FZE, and SUN PHARMACEUTICAL INDUSTRIES, LTD., Defendants.	:	C.A No. 3:14-cv-04616-MLC-TJB **FINAL JUDGMENT**

Pursuant to the Stipulation and Order to Enter Final Judgment of Noninfringement Based on Court's Claim Construction entered on June 9, 2016 (D.E. 124),

IT IS on this 6th day of ~~June~~ July 2016,

ORDERED that Final Judgment is hereby entered in favor of Defendants and against Plaintiffs in accordance with the Stipulation and Order (D.E. 124).

Mary L. Cooper
HON. MARY L. COOPER
United States District Judge

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED, TAKEDA PHARMACEUTICALS U.S.A., INC., and TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. SUN PHARMA GLOBAL FZE, and SUN PHARMACEUTICAL INDUSTRIES, LTD., Defendants.	C.A No. 3:14-cv-04616-MLC-TJB **STIPULATION AND ORDER TO ENTER FINAL JUDGMENT OF NONINFRINGEMENT BASED ON COURT'S CLAIM CONSTRUCTION**

This Stipulation and Order is entered into by and between Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals U.S.A., Inc., and Takeda

(D.I. 36), pursuant to which all Patents-in-Suit other than the '994 Patent were dismissed with prejudice on the terms and conditions set forth in the Stipulation; and

WHEREAS, Takeda filed its Second Amended Complaint[1] (D.I. 42) on February 26, 2015, asserting infringement of the '994 Patent; and

WHEREAS, on March 18, 2015, Sun filed its Answer to the Second Amended Complaint, denying the material allegations thereof and asserting various defenses and a Counterclaim seeking a declaratory judgment of noninfringement of the '994 Patent (D.I. 43); and

WHEREAS, on April 6, 2015, Takeda filed its Answer to Sun's Counterclaim (D.I. 48); and

WHEREAS, Takeda and Sun thereafter exchanged proposed claim constructions, infringement and noninfringement contentions, and engaged in fact and expert discovery with respect to claim construction; and

WHEREAS, the parties filed a Revised Joint Claim Construction and Prehearing Statement on April 23, 2015 (D.I.51) (the "Joint Construction"), which set forth, *inter alia*, each of Takeda's and Sun's respective constructions for the following limitation, which appears in asserted claim 1 and claim 29 of the '994 Patent, and are therefore also included in the asserted claims that depend from claim 1 (claims 2-4, 6-9, 13-18, 21, 23-24, 26 and 27) and claim 29 (claims 30-33, 36-40, and 43):

> "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained release agent"

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[1] Takeda's Amended Complaint (D.I. 38) inadvertently identified Caraco as a defendant. Takeda's Second Amended Complaint (D.I. 42) removed Caraco as a party to this litigation. *See* D.I. 40, Stipulation and Order to Amend Case Caption.

; and

WHEREAS, below is a table setting forth each party's proposed construction for the limitation in dispute as set forth in the Joint Construction:

Claim Language	**Sun's Proposed Construction**	**Takeda's Proposed Construction**
"an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent"	"an enteric coating layer comprising two discrete components (i.e., not chemically the same) in an admixture, namely a first component which is an enteric coating agent and a second component which is a sustained-release agent. Eudragit L30D-55 is not a sustained-release agent."	The "enteric coating layer" may be constructed by plural (e.g., 2 or 3) layers and includes a first component that is an "enteric coating agent" which can be a methacrylate copolymer and a second component that is a "sustained-release agent" which can be a methacrylate copolymer.

WHEREAS, a *Markman* claim construction hearing was held on December 2, 2015, at the conclusion of which the Court rendered its construction and opinion in a bench ruling on the record, (D.I. 76); and

WHEREAS, the Court ruled that the disputed claim language should be construed as follows: "an enteric coating layer comprising two discrete components (i.e., not chemically the same), namely a first component which is an enteric coating agent and a second component which is a sustained-release agent," (the "Enteric Coating Layer Construction") (D.I. 75); and

WHEREAS, by letter motion dated January 20, 2016, addressed to Hon. Tonianne J. Bongiovanni, U.S.M.J., Takeda sought leave to amend its infringement contentions ("Amended Contentions") pursuant to L. Pat. R. 3.7 (the "Motion to Amend"), to address the Enteric Coating Layer Construction; and

WHEREAS, on February 1, 2016, Sun filed its Opposition to Takeda's Motion to Amend (D.I. 78); and

WHEREAS, by Memorandum Opinion dated March 4, 2016, the Magistrate Judge denied the Motion to Amend for the reasons set forth in her Memorandum and Opinion (D.I. 82), and entered an Order to that effect (D.I. 83); and

WHEREAS, on March 18, 2016, (D.I. 85), Takeda filed a Notice of Motion to Appeal the Order Denying the Motion to Amend, and papers in support thereof; and

WHEREAS, on March 23, 2016, (D.I. 88), Sun filed a Motion for Summary Judgment of Noninfringement, which was based on the Enteric Coating Layer Construction; and

WHEREAS, on April 4, 2016, (D.I. 96), Sun filed its papers in Opposition to Takeda's Appeal of the denial of the Motion to Amend; and

WHEREAS, by Order dated April 7, 2016, (D.I. 99), the Court denied without prejudice Sun's Motion for Summary Judgment, with leave to move again for summary judgment after the Court's ruling on Takeda's Motion to Amend; and

WHEREAS, on April 11, 2016, (D.I. 101), Takeda filed its Reply Papers in Further Support of its Appeal of the Denial of the Motion to Amend; and

WHEREAS, on April 15, 2016, (D.I. 104), Sun filed a letter motion to strike certain portions of Takeda's Reply Papers; and

WHEREAS, on April 18, 2016, (D.I. 106), Takeda filed a letter opposing Sun's motion to strike; and

WHEREAS, by Order dated April 28, 2016 (D.I. 113), the Court denied Takeda's Motion to Amend, for the reasons set forth in its Memorandum Opinion of the same day (D.I. 112); and

WHEREAS, Takeda and Sun agree that Takeda cannot pursue its infringement claims against Sun on the '994 Patent based on (a) the current formulation of Sun's ANDA product as set forth in its ANDA No. 206013, and (b) Takeda's infringement contentions without the amendments Takeda sought to make to such contentions, but which were rejected by the Court in denying Takeda's Motion to Amend;[2] and

WHEREAS, Takeda wishes to appeal the Court's Enteric Coating Layer Construction to the United States Court of Appeals for the Federal Circuit (the "Federal Circuit"), and to preserve its right to pursue infringement claims of the '994 Patent in the event the Federal Circuit reverses or modifies the Enteric Coating Layer Construction, or reverses the Court's ruling on the Motion to Amend; and

WHEREAS, Sun wishes to preserve its rights to re-assert counterclaim or defenses (including, but not limited to, non-infringement and invalidity) against Takeda based on the '994 Patent in the event the Federal Circuit reverses or modifies the Enteric Coating Layer Construction, or reverses the Court's ruling on the Motion to Amend; and Takeda reserves all rights to oppose any such efforts by Sun.

NOW, THEREFORE, it is hereby stipulated and agreed, by and between Takeda and Sun, by their undersigned attorneys, that:

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[2] Sun does not believe that Takeda may maintain infringement claims against Sun on the '994 Patent even if the Court had granted Takeda's Motion to Amend for at least the reasons set forth in its summary judgment motion, (D.I. 88.) Takeda believes its Amended Contentions would state a meritorious claim against Sun for infringement of the '994 Patent. (D.I. 99.) The Court while denying Sun's Motion for Summary Judgment without prejudice observed that the Plaintiff's appeal of the Magistrate Judge's Order dated March 4, 2016 is pending and granted the defendant leave to move again for Summary Judgement upon a new notice of motion and new supporting papers after the Court resolves the appeal from the March 4, 2016 Order of the Magistrate Judge.

1. For purposes of this Stipulation and Order, "Instant Action" shall mean the claims, defenses, and counterclaims regarding Sun's ANDA No. 206013 as of its submission to the U.S. Food and Drug Administration ("FDA") on July 29, 2013 and formulations disclosed therein, as well as any changes to ANDA No. 206013 that are made subsequent to July 29, 2013, that would not alter the infringement analysis under the '994 Patent.

2. Based on the Enteric Coating Layer Construction, Final Judgment shall be entered in favor of Sun and against Takeda on Takeda's claims in the Instant Action against Sun for infringement of claim 1 and claim 29 of the '994 Patent, and the asserted claims that depend from claim 1 (claims 2-4, 6-9, 13-18, 21, 23-24, 26 and 27) and claim 29 (claims 30-33, 36-40, and 43).

3. Based on the Enteric Coating Layer Construction, (a) Final Judgment shall be entered in favor of Sun and against Takeda on Sun's counterclaim in the Instant Action against Takeda for non-infringement of the '994 Patent; and (b) all of Sun's other defenses not accounted for in this Stipulation shall be dismissed without prejudice with the right, should an appeal result in a remand and reversal, to re-assert such dismissed defenses without motion to the Court.

4. Takeda does not waive, and expressly reserves, all rights to assert infringement claims in the context of any action, other than the Instant Action, that may be commenced in the future against Sun based on the '994 Patent. Sun reserves all rights to oppose any such efforts by Takeda.

5. Sun does not waive, and expressly reserves, all rights to (a) argue in any action that Takeda commences in the future against Sun based on the '994 Patent that such action is barred, without limitation by estoppel and/or issue/claim preclusion; and (b) commence a

declaratory judgment or assert by counterclaim or defense that any claim of the '994 Patent is not infringed, invalid or unenforceable in any action. Takeda reserves all rights to oppose any such efforts by Sun.

6. Takeda does not waive, and expressly reserves, all rights to appeal to the Federal Circuit (a) this Court's Enteric Coating Layer Construction, and (b) the Court's denial of Takeda's Motion to Amend. Sun reserves all rights to oppose any such efforts by Takeda.

7. In the event that the Federal Circuit reverses and/or modifies the Enteric Coating Layer Construction, Takeda expressly reserves all rights to pursue its infringement claims against Sun on the '994 Patent based on any new or different claim construction as might be adopted by the Federal Circuit, or by this Court on remand from the Federal Circuit. Sun reserves all rights to oppose any such efforts by Takeda.

8. In the event that the Federal Circuit reverses and/or modifies the Enteric Coating Layer Construction, Sun expressly reserves all rights to pursue any counterclaims (e.g., non-infringement or invalidity) and any defenses against Takeda on the '994 Patent based on any new or different claim construction as might be adopted by the Federal Circuit, or by this Court on remand from the Federal Circuit. Takeda reserves all rights to oppose any such efforts by Sun.

9. In the event that the Federal Circuit directs this Court to grant Takeda's Motion to Amend, Takeda expressly reserves all rights to pursue its infringement claims against Sun on the '994 Patent based on Takeda's Amended Contentions. Sun reserves all rights to oppose any such efforts by Takeda.

10. In the event that the Federal Circuit directs this Court to grant Takeda's Motion to Amend, Sun expressly reserves all rights to pursue counterclaims (e.g., non-infringement or invalidity) and any defenses against Takeda on the '994 Patent to defend against Takeda's

Amended Contentions, including, but not limited to, by requesting that the Court reopen fact discovery, allow for supplemental non-infringement and invalidity contentions, and redo *Markman*. Takeda reserves all rights to oppose any such efforts by Sun.

11. Subject to any estoppel or claim/issue preclusion that may apply, Takeda and Sun each expressly reserves the right to argue for a construction different from the Enteric Coating Layer Construction in any future case involving Takeda and Sun, or Takeda and any other entity, or Sun and any other entity.

12. On April 29, 2016, Takeda served the expert reports of Dr. David Bugay and Dr. Stephen Byrn. Those reports set forth the bases for Takeda's infringement position on the asserted claims of the '994 Patent, based on 1) the Enteric Coating Layer Construction and 2) Takeda's proposed amended infringement contentions which the Court did not permit. Sun believes that these two expert reports violated certain Court Orders by including expert opinions based on infringement contentions that the Court had barred. (D.I. 82-83, 112-113; *see also* D.I. 119.) Takeda believes it was proper to serve the reports. Sun requested that Takeda withdraw them. At Sun's request, Takeda hereby withdraws those expert reports of Dr. David Bugay and Dr. Stephen Byrn without prejudice to Takeda seeking in the future to re-serve them based on the outcome of any Federal Circuit appeal that might be taken based on this stipulation ("The Appeal"). Sun reserves all rights to oppose any attempt by Takeda to re-serve the expert reports of Dr. David Bugay and Dr. Stephen Byrn after The Appeal; provided, however, Sun agrees that it will not use against Takeda in any such opposition the fact that Takeda withdrew the two reports identified in this stipulation.

Dated: June 8, 2016

AGREED AND STIPULATED TO:

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SO ORDERED this 9th day of JUNE, 2016.

Mary L. Cooper
Hon. Mary L. Cooper
United States District Judge

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED, et al., Plaintiffs, v. SUN PHARMA GLOBAL FZE, et al., Defendants.	CIVIL ACTION NO. 14-4616 (MLC) **O R D E R**

THE PARTIES, having filed a Joint Claim Construction and Prehearing Statement, requesting the Court to construe the claim term:

> "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent"

in claim 1 and claim 29 of United States Patent Number 6,328,994 (see generally dkt. 51) ("the '994 patent"); and the Court having conducted a Markman hearing on December 2, 2015 (see dkt. 73); and the Court having considered the parties' submissions (see dkts. 52, 53, 54, 55, 56, 57, 61, 62, 63, 64) and argument; and for the reasons stated on the record:

IT IS THEREFORE on this 4th day of December, 2015, **ORDERED** that the Court construes the term:

> "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent"

to mean:

"an enteric coating layer comprising two discrete components (i.e., not chemically the same), namely a first component which is an enteric coating agent and a second component which is a sustained-release agent."

IT IS FURTHER ORDERED that the '994 patent does not require an admixture of the two discrete components.

And it is hereby **SO ORDERED.**

s/ Mary L. Cooper
MARY L. COOPER
United States District Judge

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED, TAKEDA PHARMACEUTICALS U.S.A., INC., and TAKEDA PHARMACEUTICALS AMERICA, INC.,

Plaintiffs,

-vs-

SUN PHARMA GLOBAL FZE, SUN PHARMACEUTICAL INDUSTRIES, LTD., and CARACO PHARMACEUTICAL LABORATORIES, LTD.,

Defendants.

CIVIL ACTION NUMBER:
3:14-cv-04616(MLC)

MARKMAN HEARING

SEALED TRANSCRIPT OF PROCEEDINGS

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
December 2, 2015

B E F O R E: THE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.
/S/ Regina A. Berenato-Tell, CCR, CRR, RMR

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where it is stated that that was what the '994 patent is limited to. It does teach as a blend. The patent teaches several examples, and, so, you know, I think that to somehow imply that the patent is limited to this one sentence in our expert's declaration I think that that is misleading and inappropriate, particularly given the fact that an admixture is nowhere defined as part of the definition for enteric coating layer within the patent, and, so, there is no requirement, your Honor, of a blend or an admixture of an enteric coating agent and sustained-release agent within a given enteric coating layer.

With that, I think that that is it, unless your Honor has some questions for me in light of Sun's presentation.

THE COURT: I don't.

MS. CHOW: Thank you.

MR. LOCKNER: Nothing further from Sun, your Honor.

THE COURT: Okay. I'm going to rule.

I am not going to make a ruling at this claim construction stage as to whether L30D-55 is a sustained-release agent within the meaning of Claim 1 or Claim 29 of the '994 patent-in-suit.

The claim language itself that you have asked me to focus on does not mention that substance, and the prosecution history, while it does include descriptions of that substance, I find nowhere constitutes, on the part of the patentee, a clear and manifest disavowal that L30D-55 could be a sustained-release agent within the meaning of the claim language that was ultimately approved.

This issue will survive today, and we will deal with it in the infringement context. And, if necessary, I will revisit it. But I have read every single scrap of the expert declarations. I have carefully read the patent and its specification. And I have read the entire prosecution history that I have been given, including the excerpts that are supplied in the parties' slides.

I think that Sun has a very strong argument that L30D-55 will not be seen to be a sustained-release agent for purposes of an infringement analysis, but I do not find it necessary for the Court to construe that particular substance as to whether it qualifies as a sustained-release agent within the meaning of the disputed claim language here.

I realize that this is a very major, pivotal bone of contention between the parties, but I don't find it to be appropriate for claim construction for the reasons that I have stated.

I do find that a fair reading of the claim language, in light of the specification and the prosecution history, favors Sun's position that we should read the disputed claim language to require it to comprise two discrete components that are not chemically the same. When the patent applicant attempted to in a way gloss over whether the enteric coating layer had both an enteric coating agent and a sustained-release agent, they got a second rejection for that. It was only when the applicant redrafted to have this claim language say, "comprising a first component, which is an enteric coating agent and a second component which is a sustained-release agent," that the patent was approved.

The prosecution history ends, of course, with the notice of allowance of the patent, and the explanation by the examiner -- Notice of Allowability, Exhibit 14 to Mr. Carpenter's declaration that begins at Docket Entry 55-1. The examiner had three problems, basically, with the application as it originally stood. First, it did not identify the active pharmaceutical ingredient. Second, there was no hardness criteria for the tablet. And, third, the enteric coating layer was already present in the prior art '212 patent.

After all the prosecution history where those three problems were addressed by the applicant, both in amendments and in argument, the final statement in the Notice of Allowance only talked about that third criteria, the two-component aspect. The complete statement of the examiner is correctly quoted at Sun's Slide 60, and here I quote from Page 2 of the Notice of Allowance, which is entitled, "Reasons for Allowance." And it has a number one, Paragraph Number 1, and it says, and I quote, "The following is an examiner's statement of reasons for allowance: The cited prior art does not fairly teach or suggest an oral composition comprising a first component which is an enteric coating and a second component which is a sustained-release agent." That's the only topic the examiner talked about in finally, finally allowing the amendments to overcome the prior rejections.

So, it is very clear that this two-component aspect was material to the examiner's approval of the patent over the objections about the enteric coating layer being old prior art.

If you look carefully at that sentence you can see the examiner didn't say it exactly right, but he had the concept, basically. And, so, I find that you can't tell whether an accused composition infringes the patent unless you can tell that it has two discrete components. And in order to be able to tell that it has two discrete components within the language and specification and prosecution history, they at least have to be chemically distinguishable.

I do recognize that each one of the examples in the patent has chemically distinguishable ingredients when it comes to the enteric coating layer, but I'm not basing my ruling about that on the fact that these nine examples have two ingredients. I'm basing it on the fact that you just simply have to have two ingredients in order to be able to practice this invention; two ingredients in the enteric coating layer as defined in the claim language, Claim 1 and Claim 29.

Whether they have to be admixed, I don't think they do. The patent is absolutely silent on that. The examples certainly admix the enteric coating agent and the delayed release action in each one of the examples, but that does not appear to be integral, necessary to the practicing of this invention as reflected in the examples. Nor does the specification suggest that these two components of the enteric coating layer have to be ground up, mixed together, and sprayed on as one mixture.

In the specification the primary description of the enteric coating layer is seen at Column 9 starting with Line 8, and continuing all the way down to Line 35, but mostly terminating at Line 26. And we know that the specification wasn't changed, even though the claim language had to change during patent prosecution. So, we have to read the specification in light of the claim language.

But the notion was in the specification that you have an enteric polymer agent, and you have a sustained-release agent, and a water soluble polymer, and plasticizers, and mixtures of the examples of plasticizers. You would probably have all of that together in your enteric coating layer, but these are all optional as stated in the specification. It says, "includes, for example," with lots of "et ceteras" thrown in.

I am very mindful that the specification in Column 9, Lines 30 through 35, talks about how much enteric coating agent and how much controlled release agent you're going to use; and there is a concept in this patent that the granule has to survive into the GI tract. So if you don't have enough enteric functionality to get it through the stomach with the drug intact, then you're not practicing this invention. So, there is definitely a need for an enteric coating layer that can in fact be an enteric coating layer.

But whether the sustained-release agent has to be mixed together with the enteric agent before applying it to the granule as an enteric coating layer, really the patent is silent, and I'm not going to read that kind of a requirement in as a matter of claim construction.

I think Takeda makes a pretty good point that the word "admixture" is found elsewhere in the patent, certainly in some of the methodology language, and we're not dealing with a method claim here, a method of manufacture claim. We're dealing with composition claims here. But we don't see the word "admixture" applied to these two components of the enteric coating layer.

So, here's my ruling: "An enteric coating layer comprising two discrete components (i.e., not chemically the same) namely," and then just quote the rest of the claim language unchanged. "A first component which is an enteric coating agent and a second component which is a sustained-release agent."

I am making no ruling as to whether Eudragit L30D-55 is or is not a sustained-release agent within the meaning of this claim language, and I am ruling that the patent does not require an admixture in any one layer of the enteric coating layer.

I have made this ruling on the basis of the intrinsic evidence. I have considered all of the extrinsic evidence, all of it, all of the declarations of the two experts, which are found at Docket Entry 54 and 64 for plaintiff's expert Dr. Byrn, and Docket Entry 53-1 and 61-8 for defendant's expert Dr. Banakar, and I have considered their declarations, as well as the extrinsic treatises and materials that they cite. But I don't find it necessary to elaborate further in rendering my ruling by weighing the credibility of the experts on these three disputed points. I find that the intrinsic evidence, as generally informed by the tutorial that these experts have given me, is sufficient for me to understand the limited claim construction issues that I'm ruling on from the perspective of what would be the hypothetical person of ordinary skill in the art at the time of the patent application.

I notice that the parties somewhat differ in their description of the person of ordinary skill in the art, but the parties have not presented to me a dispute requiring that we resolve their discrepancy. Dr. Banakar would have a Ph.D. type, and Dr. Byrn would have a bachelor degree type, but they each would have three or four years of experience in very highly specialized drug formulation studies and analyses of this type. So, I don't think I need to resolve the POSA definition difference in making a claim construction ruling.

I do agree with the parties that the priority date for purposes of looking at the prior art is as they stated, May 17, 1999.

This will be in lieu of a written opinion. If I have to get into whether Eudragit L30D-55 is or is not a sustained-release agent based upon the evidence at trial, that will receive a written opinion.

I'll prepare the order. Is this sufficient, counsel, for you to move forward with enough guidance at this point?

MS. CHOW: Yes, your Honor.

MR. LOCKNER: Yes. Thank you, your Honor.

THE COURT: Okay. All right. Thank you, everyone. Oh, sealed, unsealed?

MR. LOCKNER: Sealed.

MS. CHOW: Sealed.

THE COURT: That's fine. Okay. Good.

(Proceedings concluded at 1:15 p.m.)

US006328994B1

(12) United States Patent
Shimizu et al.

(10) Patent No.: US 6,328,994 B1
(45) Date of Patent: Dec. 11, 2001

(54) **ORALLY DISINTEGRABLE TABLETS**

(75) Inventors: **Toshihiro Shimizu**, Itami; **Shuji Morimoto**; **Tetsuro Tabata**, both of Suita, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/355,781**

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§ 371 Date: **Aug. 4, 1999**

§ 102(e) Date: **Aug. 4, 1999**

(87) PCT Pub. No.: **WO99/59544**

PCT Pub. Date: **Nov. 25, 1999**

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Jan. 12, 1999	(JP)	11-005144
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(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/20; A61K 9/46; A61K 9/16

(52) **U.S. Cl.** **424/489**; 424/464; 424/465; 424/466; 424/490; 424/493

(58) **Field of Search** 424/464, 465, 424/466, 489, 490, 493

(56) **References Cited**

U.S. PATENT DOCUMENTS

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(57) **ABSTRACT**

An orally disintegrable tablet, of the present invention, which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive, has superior disintegrability or dissolution in the oral cavity so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged or children and easily administered without water. Also, because the tablet of the present invention contains fine granules having the average particle diameter such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration.

45 Claims, No Drawings

ORALLY DISINTEGRABLE TABLETS

This application is a 371 of PCT/JP99/02548 filed May 17, 1999.

This application is the National Stage of International Application Serial No. PCT/JP99/02548, filed May 17, 1999.

TECHNICAL FIELD

The present invention relates to an orally disintegrable tablet having a characteristic of fast disintegration in the oral cavity even without water.

BACKGROUND ART

Pharmaceutical solid preparations, for example, tablets, usually are prepared to make pharmaceutically active ingredients absorb in a digestive organ by disintegration or dissolution through oral administration, without fast disintegration or dissolution in the Qral cavityl

JP-A-6-502194 (U.S. Pat. No. 5,464,632) discloses a rapidly disintegrable multiparticulate tablet, the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the active substance, weight percentage of the active substance in the excipient mixture, or the size of the coated microgranule.

On the other hand, JP-A-5-92918 discloses a powder consisting of a fine-particle core coated with a water-soluble high molecular compound and at least one physiologically active substance, and having a granule size of practically up to 500 μm. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the physiologically active substance, weight percentage of the active substance in the coated granule or the size of the coated granule.

JP-A-63-301816 and U.S. Pat. No. 5,026,560 disclose spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose. However, there is no disclosure of an orally disintegrable tablet.

EP-A-0452862 discloses a spherical granule obtained by coating a pharmacologically inactive spherical seed core having at least 50 weight % microcrystalline cellulose and an average particle size of 100–1000 μm, with a powder comprising an active ingredient, by using an aqueous binding solution, and spraying an aqueous solution or suspension of a coating agent thereon. However, most of the particle sizes of thus obtained granules are 500 μm or more.

JP-A-1-268627, JP-A-1-268628 and JP-A-8-27033 disclose pharmaceutical compositions using erythritol, respectively. However, there is no disclosure of a solid pharmaceutical composition characterized by fast disintegration in the oral cavity.

JP-A-9-48726 discloses a buccal formulation consisting of a drug and a substance wetting in a mouldable way on humidifying, and retaining a shape after moulding and drying. As such substance, sugars, sugar alcohols and water-soluble polymers are exemplified.

JP-A-5-271054 discloses production of fast dissolving tablets comprising an active ingredient and sugars.

JP-A-9-71523 discloses a tablet with rapid disintegration in the oral cavity comprising medicine, crystalline cellulose, low-substituted hydroxypropyl cellulose and lubricant.

However, these prior art references nowhere disclose an acid-labile physiologically active substance with a basic inorganic salt as an active substance, weight percentage of the active substance in the tablet or the size of the coated fine granule.

To accompany an aging population and their changes in life environment, it is desired to develop an orally disintegrable solid preparation capable of being administered without water, retaining the convenience for use which is a characteristic of a tablet, and being administered on demand easily, anytime and anywhere, without water.

Conventional granules have large particle diameters, which results in inferior workability when dispensing, and also results in difficulties in consistently adding a regular amount of the granules when they are combined into tablet or capsules. Granules having a large particle diameter (400 μm or more of average particle diameter) also produce a feeling of roughness in the mouth. Accordingly, especially when used in an orally disintegrable tablet, the average particle a diameter of the included granules must be about 400 μm or less, preferably about 350 μm.

For many reasons, such as, masking a bitter taste, or providing enteric abilities or release abilities, it is desirable to prepare the solid pharmaceutical preparations as granules (or fine granules), In particular, in case of granules or fine granules in which the active ingredient of the drug is enteric coated to impart enteric dissolution, there is a need for enteric coating to prevent dissolution by stomach acid (i.e., to make the preparation acid-resistance). It is necessary to coat the whole surface of the particle—before the enteric coating—(including a case of the crystal of physiologically active substance only, and a case of the granule produced by granulation), with the enteric coating. Namely, at least some uniform thickness (at least 20 μm or more) of the coating layer is needed. Even a portion of thin and weak coating, is undesirable because acid-resistance is lowered. Accordingly, before the enteric coating, it is necessary that the particle is as spherical with as smooth a surface as possible in form, as uniform as possible in size, and has less cavities.

It is very difficult to produce an enteric coated fine granule with an average particle diameter of 400 μm or less, when the coating is performed no that at least 20 μm thickness of coating layer may coat the whole particle, and the enteric coated particle contains a basic inorganic salt for stabilization of an acid-labile physiologically active substance, and where it contains binders for maintaining the strength of the particle and/or disintegrants for maintaining the disintegrability (dissolution) of the particles. Further, in the case where the content of the acid-labile physiologically active substance is increased, it is necessary to also increase the content of the excipients such as basic inorganic salt, binders and disintegrants. Furthermore, it is very difficult to produce a small enteric coated fine granule containing the physiologically active substance in high content.

Accordingly, it is desired to develop a fine granule which is coated with the enteric coating layer on the composition containing the physiologically active substance such as a physiologically active substance containing a basic inorganic salt and which has a particle diameter so that roughness or oral discomfort is not felt, to develop a fine granule containing the physiologically active substance, i.e., the active ingredients of drugs, and so forth, in high content, to develop a fine granule while maintaining enteric dissolution, a disintegrability and dissolution and suitable strength, and to develop an orally disintegrable preparation containing such a fine granule, being a fast disintegration type, showing superior oral disintegrability and dissolution and having suitable strength (hardness) so that it will not be damaged through production processes or handling.

In particular, there is a need to combine an acid-labile physiologically active substance, with basic inorganic salts and so forth for stability, and further to coat with coating layers such as an enteric layer. In such cases, it is an important problem to produce an small enteric coated fine granule, even though it contains the acid-labile physiologically active substance in high concentration and in high content.

DISCLOSURE OF INVENTION

The present invention relates to:

[1] an orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive;

[2] an orally disintegrable tablet of the above [1], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[3] an orally disintegrable tablet of the above [1], wherein the fine granules further comprise a basic inorganic salt;

[4] an orally disintegrable tablet of the above [1], wherein the additive comprises a water-soluble sugar alcohol;

[5] an orally disintegrable tablet of the above [1], wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol;

[6] an orally disintegrable tablet of the above [4], wherein the additive comprises (i) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose;

[7] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 425 μm or less;

[8] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 400 μm or less;

[9] an orally disintegrable tablet of the above [1], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[10] an orally disintegrable tablet of the above [9], wherein the benzimidazole compound is lansoprazole;

[11] an orally disintegrable tablet of the above [3], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[12] an orally disintegrable tablet of the above [1], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[13] an orally disintegrable tablet of the above [12], wherein the core comprises 50 weight % or more of lactose;

[14] an orally disintegrable tablet of the above [12], wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose;

[15] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance;

[16] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance;

[17] an orally disintegrable tablet of the above [1], wherein the fine granules are produced by fluidized-bed granulation method;

[18] an orally disintegrable tablet of the above [1], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[19] an orally disintegrable tablet of the above [18], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[20] an orally disintegrable tablet of the above [18], wherein the enteric coating layer further comprises a sustained-release agent;

[21] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is a methacrylate copolymer;

[22] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[23] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is erythritol;

[24] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is mannitol;

[25] an orally disintegrable tablet of the above [5], wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules;

[26] an orally disintegrable tablet of the above [4], wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule;

[27] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %;

[28] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 5.0 to 7.0 weight %;

[29] an orally disintegrable tablet of the above [1], which further comprises crospovidone;

[30] an orally disintegrable tablet of the above [1], wherein the oral disintegration time is one minute or less;

[31] an orally disintegrable tablet of the above [1], which comprises no lubricant inside the tablet;

[32] fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt;

[33] fine granules of the above [32], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[34] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 425 μm or less;

[35] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 400 μm or less;

[36] fine granules of the above [32], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[37] fine granules of the above [36], wherein the benzimidazole compound is lansoprazole;

[38] fine granules of the above [32], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[39] fine granules of the above [32], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[40] fine granules of the above [39], wherein the core comprises 50 weight % or more of lactose;

[41] fine granules of the above [32], wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance;

[42] fine granules of the above [32], which are produced by fluidized-bed granulation method;

[43] fine granules of the above [32], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[44] fine granules of the above [43], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[45] fine granules of the above [43], wherein the enteric coating layer further comprise a sustained-release agent;

[46] fine granules of the above [45], wherein the sustained-release agent is a methacrylate copolymer;

[47] fine granules of the above [45], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[48] fine granules of the above [32], wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules;

[49] a tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of the above [32], and so forth.

In the present specification, "coating" means also partial coating and adhesion or adsorption in addition to coating the whole surface of an object (e.g., core) which is to be coated.

"Spherical" means also forms having a curved surface such as forms having elliptic cross sections, and forms in the shapes of eggplants and drops in addition to spheres.

"Average particle diameter" means volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified. It can be measured by, for example, a laser diffraction particle distribution measurement method. Concretely exemplified is a method using Raser Diffraction Analyzer, type: HEROS RODOS [trade name; manufactured by Sympatec (Germany)].

"An orally disintegrable tablet" of the present invention comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive.

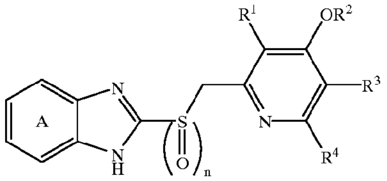
In the present invention, "fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance" have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth. Preferably, the average particle diameter of the fine granules is 300 to 400 μm.

Aside from the average particle diameter of the above "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 425 μm, more preferably 300 to 400 μm.

"Practically" as used in "the particle diameter is practically 425 μm or less" and "the particle diameter is practically 400 μm or less" means that the particles may include a small quantity (about 5 weight % or less) of particles whose particle diameter Is out of above described range to Include the inevitable contaminant particles.

"An acid-labile physiologically active substance" includes a compound being unstable in an acidic region and/or a compound inactivated by an acid, especially a pharmaceutical ingredient. Concretely mentioned are vitamins such as vitamin B_{12}, fursultiamine, folic acid, vitamin A, vitamin D, as well as a known benzimidazole compound having an antiulcer activity of the formula (I) below, or a salt thereof.

Formula (I)



wherein ring A may be substituted; R^1, R^3 and R^4 are the same or different and each is a hydrogen, an alkyl or an alkoxy; R^2 is C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy; and n is 0 or 1.

In the above formula (I), "substituent(s)" of the "substituted ring A" include, for example, halogen, C_{1-10} alkyl which may be substituted, C_{3-7} cycloalkyl which may be substituted, C_{2-16} alkenyl which may be substituted, C_{1-10} alkoxy which may be substituted, cyano, carboxy, C_{1-7} alkoxycarbonyl, C_{1-4} alkoxycarbonyl-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-14} alkyl, hydroxy, hydroxy-C_{1-7} alkyl, C_{1-6} acyl, carbamoyloxy, nitro, C_{2-6} acyloxy, C_{6-12} aryl, C_{6-12} aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, etc.

The "substituent" of the above "C_{1-10} alkyl which may be substituted", "C_{3-7} cycloalkyl which may be substituted", or "C_{2-16} alkenyl which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, (6) carbamoyl, etc. The number of these substituents is 1 to 3.

The "substituent" of the above "C_{1-10} alkoxy which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, etc. The number of these substituents is 1 to 3.

The above "C_{1-6} acyl" includes, for example, C_{2-6} alkanoyl such as formyl, acetyl, propionyl, etc.

The above "C_{1-4} acyl" includes, for example, formyl and C_{2-4} alkanoyl such as acetyl, propionyl, etc.

The above "C_{2-6} acyloxy" includes, for example, C_{2-6} alkanoyloxy such as acetyloxyl, etc.

The above "C_{6-12} aryl" includes, for example, phenyl, naphthyl, etc.

The above "C_{6-12} aryloxy" includes, for example, phenoxy, naphthyloxy, etc.

The "alkyl" for R^1, R^3 or R^4 includes, for example, a straight-chain or branched C_{1-10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc. Among others, preferred is a straight-chain or branched C_{1-6} alkyl. More preferred is a straight-chain or branched C_{1-3} alkyl.

The "alkoxy" for R^1, R^3 or R^4 includes, for example, C_{1-10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy, cyclohexyloxy, etc. Among others, preferred is C_{1-6}alkoxy. More preferred is C_{1-3} alkoxy.

The "C_{1-4} alkyl" of the "C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy" for R^2 includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc.

The "C_{1-4} alkoxy" of the above "C_{1-4} alkyl which may be substituted by a C_{1-4} alkoxy" includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.

The number of the substituents which the "C_{1-4} alkyl" has is preferably 1 to 3.

Salts of the benzimidazole compound include pharmaceutically acceptable salts such as alkali metal salts, e. g., sodium salts and potassium salts, alkaline earth metal salts e. g., calcium salts and magnesium salts, etc.

Such benzimidazole compounds having an antiulcer activity, or salts thereof include, for example, a compound or a salt thereof disclosed in JP-A-52-62275, JP-A-54-141783 JP-A-57-53406, JP-A-58-135881, JP-A-58-192880, JP-A-59-181277, JP-A-61-50978, JP-A-62-116576, JP-A-62-277322, JP-A-62-258320, JP-A-62-258316, JP-A-64-6270, JP-A-64-79177, JP-A-5-59043, JP-A-62-111980, JP-A-5-117268, EP-A-166287, EP-A-519365, and so forth.

The "physiologically active substance" of the present invention preferably is a benzimidazole compound or a salt thereof such an tenooprdzole, omneirazole, rabmprazole, pantoprazole, perprazole, leminoprazole, TU-199, etc. Preferred is lansoprazole and omeprazole, etc. More preferred is lansoprazole.

The amount of the "acid-labile physiologically active substance" in the "composition" is, for example, about 10 weight % or more, preferably about 20 weight % or more, more preferably about 23 weight % or more, especially preferably about 25 weight % or more. Among others, preferred is 20 to 50 weight %.

In the "composition", a basic inorganic salt is preferably incorporated with the acid-labile physiologically active substance.

The "basic inorganic salt" includes, for example, a basic inorganic salt of sodium, potassium, magnesium and/or calcium, preferably a basic inorganic salt of magnesium and/or calcium. Among others, preferred is a basic inorganic salt of magnesium.

The basic inorganic salt of sodium includes, for example, sodium carbonate, sodium hydrogencarbonate, etc.

The basic inorganic salt of potassium includes, for example, potassium carbonate, potassium hydrogencarbonate, etc.

The basic inorganic salt of magnesium includes, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metagilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite $[Mg_6Al_2(OH)_{16}.CO_3.4H_2O]$, aluminum magnesium hydroxide $[2.5MgO.Al_2O_3.xH_2O]$, etc. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

The basic inorganic salt of calcium includes, for example, precipitated calcium carbonate, calcium hydroxide, etc.

The preferable examples of the "basic inorganic salt" include heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

Such basic inorganic salt of magnesium or calcium, etc. has a basic pH (not less than 7) when it is in the form of a 1% aqueous solution or suspension.

Two or more of these basic inorganic salts (preferably a basic inorganic salt of magnesium, a basic inorganic salt of calcium, etc.) can be used as a mixture in a given ratio. The amount of the basic inorganic salt to be used is appropriately selected depending on the kind of the basic inorganic salt and is, for instance, about 0.3 to 200 weight %, preferably about 1 to 100 weight %, more preferably about 10 to 50 weight %, especially preferably about 20 to 40 weight % relative to the benzimidazole compound or a salt thereof.

The "composition" may contain water-soluble polymers, the following binders, lubricants, and excipients, etc. in common use as pharmaceutical materials. The amount of such water-soluble polymers, binders, lubricants, and excipients is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "water-soluble polymer" includes, for example, a water-soluble polymer which is soluble in ethanol (i.e., an ethanol-soluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropyl cellulose, which may be referred to as "HPC" hereinafter), poly(vinylpyrrolidone), etc.; a water-soluble polymer which is insoluble in ethanol (i.e., an ethanol-insoluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropylmethyl cellulose, which may be referred to as "HPMC" hereinafter, methyl cellulose, carboxymethyl cellulose sodium, etc.), sodium polyacrylate, polyvinyl alcohol, sodium alginate, and guar gum, etc.

When such water-soluble polymers are used, the dissolution of drugs (physiologically active substances) can be controlled by employing them in combination with the ethanol-soluble water-soluble polymer and ethanol-insoluble water-soluble polymer or by employing them in combination with some water-soluble polymers having different viscosity.

In the present invention, the "water-soluble polymer" is preferably, a cellulose derivative such as HPC, HPMC, and methyl cellulose, and polyvinyl alcohol. More preferred is a cellulose derivative such as HPC, HPMC.

The "HPC" contains, for example, about 53.4 to 77.5 weight %, more preferably about 60 to 70 weight %, of hydroxypropoxyl group. The viscosity of 2 weight % aqueous solution of HPC at 20° C. is usually about 1 to 150,000 cps (centipoise). As the above HPC, hydroxypropyl cellulose defined in Japanese Pharmacopoeia may be employed. Hereinafter, all viscosity of HPC is a value of 2 weight % aqueous solution at 20° C.

The "HPMC" is a mixed ether which is connected by a methoxy group and a hydroxypropoxy group. The content of the methoxy group of HPMC is, for example, about 19 to 30 weight %, The content of the hydroxypropoxy group is, for example, about 4 to 12 weight %. The viscosity of 2 weight % aqueous solution of HPMC at 20° C. is usually about 1 to 40,000 centistokes. As such HPMC may be employed hydroxypropylmethyl cellulose 2208 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2906 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2910 defined by Japanese Pharmacopoeia, and so forth. Hycroxypropyl cellulose(s) may be employed alone or in admixture of two or more thereof.

The content of the water-soluble polymer such as HPC and/or HPMC is usually about 0.1 to 50 weight %, preferably about 1 to 30 weight %, as against the whole "composition" containing the physiologically active substance, in order to control the dissolution of the physiologically active substance in the composition containing the physiologically active substance and retain a high content of the physiologically active substance.

The above "enteric coating layer" which coats the "composition having 10 weight % or more of an acid-labile physiologically active substance" includes, for example, an aqueous enteric polymer agent such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (hereinafter, referred to as HP-55), hydroxymethyl cellulose acetate succinate, methacrylate copolymer [e.g., Eudragit L30D-55 etc. (trade name; manufactured by Rohm GmbH (Germany)), KollICoat MAE30DP (trade name; manufactured by BASF (Germany)), Polyquid PA-30 (trade name; manufactured by SanyoKasei (Japan)), etc.], carboxymethyl cellulose, shellac, etc.; a sustained-release agent such as methacrylate copolymer [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; a water-soluble polymer; plasticizers such as triethyl citrate, polyethylene glycol, acetylatedmonoglyceride, triacetin, castor oil, etc. and mixtures thereof.

The "aqueous enteric polymer agent" is preferably a methacrylate copolymer. The "sustained-release agent" is preferably a methacrylate copolymer.

The "sustained-release agent" is used in an amount of 5 to 30 weight %, preferably 5 to 15 weight %, relative to 100 weight % of the "aqueous enteric polymer agent". The "plasticizers" is used in an amount of 5 to 30 weight% relative to 100 weight % of the "aqueous enteric polymer agent".

The "additives" of the "orally disintegrable tablet which. comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive" may be ones commonly employed as pharmaceutical materials. The amount of such additives to be used is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "additives" include, for example, a water-soluble sugar alcohol, a crystalline cellulose, a low-substituted hydroxypropyl cellulose, as well as, binders, acids, foaming agents, artificial sweeteners, flavorants, lubricants, colorants, stabilizers, excipients, disintegrants, and so forth.

The "water-soluble sugar alcohol" means a water-soluble sugar alcohol which needs water in an amount of less than 30 ml when 1 g of water-soluble sugar alcohol is added to water and dissolved within about 30 minutes at 20° C. by strongly shaking every 5 minutes for 30 seconds.

The "water-soluble sugar alcohol" includes, for example, sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, etc. Two or more of these water-soluble sugar alcohols can be used as a mixture in a given ratio.

The "water-soluble sugar alcohol" is preferably mannitol, xylitol and erythritol. More preferred is mannitol and erythritol. Especially preferred is mannitol. As erythritol, one that is produced by fermentation with yeasts using glucose as the starting material, and that has a particle size of at most 50 mesh is used. Such erythritol is available on the market, e.g. as manufactured by Nikken Chemical Co., Ltd. (Japan).

The "water-soluble sugar alcohol" is usually employed in an amount of about 5 to 97 weight %, preferably about 10 to 90 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient strength of the preparation and sufficient disintegration or dissolution in the oral cavity.

For example, mannitol or erythritol is usually employed in an amount of about 5 to 90 weight %, preferably about 10 to 80 weight %, more preferably about 20 to 80 weight %, especially preferably about 50 to 80 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "crystalline cellulose" includes refined one having partially α-cellulose depolymerization. Such crystalline cellulose includes one called microcrystalline cellulose. Examples of the "crystalline cellulose" include CEOLUS KG801, avicel PH101, avicel PH102, avicel PH301, avicel PH302, avicel RC-591 (crystalline cellulose carmellose sodium), etc. Among these, preferably employed is CEOLUS KG801 which is also called crystalline cellulose of high compressibility. Two or more of the crystalline cellulose can be used as a mixture in a given ratio. Such crystalline cellulose is available on the market, for example, as manufactured by Asahi Chemical Co., Ltd. (Japan).

The "crystalline cellulose" is used, for instance, in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, more preferably about 5 to 20 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "low-substituted hydroxypropyl cellulose" means a low-substituted hydroxypropyl cellulose wherein the content of hydroxypropoxyl group in the hydroxypropyl cellulose (hereinafter,maybe abbreviated to "the content of HPC group") is about 5.0 to 9.9 weight %, preferably a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %, a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %, and so forth.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9% includes, for example, LH-22, LH-32 and mixtures thereof, which are commercially available [Shin-Etsu Chemical Co., Ltd. (Japan)]. Also, they can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

The low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0% includes, for example, LH-23, LH-33 and mixtures thereof, described in the following Reference Examples. They can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

At first, alkaline cellulose containing free alkaline and propylene oxide is reacted to obtain the crude low-substituted hydroxypropyl cellulose containing free alkaline.

Concretely, for example, raw material pulp such as wood pulp and cotton leader is immersed in about 10 to 50% concentration of an aqueous solution of sodium hydroxide, and pressed to obtain alkaline cellulose of which NaOH/cellulose ratio is about 0.1 to 1.2 (ratio by weight). Next, crude low-substituted hydroxypropyl cellulose containing free alkaline is obtained by reacting the resulting alkaline cellulose and propylene oxide with stirring at about 20 to 90° C. for about 2 to 8 hours. Propylene oxide is used in an amount so that the content of hydroxypropoxyl group in the desired low-substituted hydroxypropyl cellulose can be 5 or more weight % to less than 7 weight % (in case of the low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %), 7 or more weight % to less than 9.9 weight % (in case of the low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %).

The crude low-substituted hydroxypropyl cellulose containing free alkaline is dispersed in water or hot water containing about 5 to 80% of acid necessary to neutralize all the alkaline, and a part of the crude low-substituted hydroxypropyl cellulose containing free alkaline is dissolved therein. Acid is further added to neutralize the remaining alkaline.

After the neutralization, some processes such as drainage, drying and grinding are performed in accordance with conventional methods to obtain the desired low-substituted hydroxypropyl cellulose.

The particle diameter of "the low-substituted hydroxypropyl celluloses wherein the content of hydroxypropoxyl group is 5.0 to 7.0 weight %" to be used in the present invention is, for example, about 5 to 60 Sm. preferably about 10 to 40 μm, as a average particle diameter.

In the above ranges, in case that low-substituted hydroxypropyl celluloses (L-HPC) having a relatively large particle diameter (for example, L-HPC having about 26 to 40 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in disintegrability can be produced. On the other hand, in case that L-HPC having a relatively small particle diameter (for example, L-HPC having about 10 to 25 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in strength of the preparation can be produced. Accordingly, the particle diameter of L-HPC can be suitably selected according to the characteristics of the desired pharmaceutical preparation.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 5.0 to 7.0 weight %" or the "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 7. 0 to 9.9%" is usually employed in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient oral disintegrability and sufficient strength of the preparation.

The "binders" include, for example, hydroxypropyl cellulose, hyaroxypropylmethylcellulose, crystalline cellulose, α starch (pregelatinized starch), polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, low-substituted hydroxypropyl cellulose, etc. The use of crystalline cellulose as the binders provides a solid preparation which exhibits more excellent strength of a preparation while retaining excellent disintegration and dissolution in the oral cavity.

The "acids" include, for example, citric acid (e.g., citric acid anhydrous), tartaric acid, malic acid, etc.

The "foaming agents" include, for example, sodium hydrogen carbonate, etc.

The "artificial sweeteners" include, for example, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, etc.

The "flavorants" include synthetic flavorants or natural flavorants, such as lemon, lime, orange, menthol, strawberry, etc.

The "lubricants" include, for example, magnesium stearate, sucrose fatty acid ester, polyethyleneglycol, talc, stearic acid, etc.

The "colorants" include, for example, various food colorants such as Food Yellow No. 5, Food RED No. 2, Food Blue No. 2, etc., food lakes, red iron oxide, etc.

The "stabilizers" include, for example, the above-mentioned "basic inorganic salt".

The "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride, titanium oxide, etc.

The "disintegrants" include those conventionally used in the pharmaceutical field, such as (1) crospovidone, (2) super disintegrants such as croscarmellose sodium [FMC-Asahi Chemical Co., Ltd. (Japan)], carmellose calcium [Gotoku Chemical(Yakuhin), (Japan)], (3) carboxymethylstarch sodium [e.g., Matsutani Chemical Co., Ltd. (Japan)], (4) low-substituted hydroxyDropyl cellulose e.g., Shin-Etgu Chemical Co., Ltd. (Japan)], (5) corn starch, etc. Among others, preferred is, for example, crospovidone.

The "crospovidone" includes polyvinylpolypyrrolidone (PVPP), 1-vinyl-2-pyrrolidinone homopolymer, 1-ethenyl-2-pyrrolidinone homopolymer, etc, such as Kollidon CL [manufactured by BASF (Germany)], Polyplasdone XL [manufactured by ISP Ltd. (Japan)], Polyplasdone XL-10 [manufactured by ISP Ltd. (Japan)], Polyplasdone INF-10 [manufactured by ISP Ltd. (Japan)], etc. Usually crospovidone having a molecular weight of at least 1,000,000 is used.

Two or more of these disintegrants can be as a mixture in a given ratio. For example, (i) crospovidone solely, or (ii) crospovidone and another disintegrant(s) is preferably employed.

The "disintegrants" are used, for instance, in an amount of about 1 to 15 weight %, preferably about 1 to 10 weight %, more preferably about 3 to 7 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

In the present invention, the "fine granules" may contain, for example, titanium oxide as a masking agent.

The diameter of the "orally disintegrable tablet" of the present invention is about 5 to 20 mm, preferably about 7 to 15 mm, more preferably about 8 to 13 mm.

The "orally disintegrable tablet" may comprise no lubricant inside the tablet.

The "orally disintegrable tablet" of the present invention exhibits fast disintegrability or dissolubility in the oral cavity, and also an appropriate strength of preparation.

The oral disintegration time of the "orally disintegrable tablet" of the present invention (the time for healthy male or female adults to complete disintegration by buccal saliva) is one minute or less, usually about 50 seconds or less, preferably about 40 seconds or less, more preferably about 30 seconds or less.

The strength of the "orally disintegrable tablet" of the present invention (measurement with a tablet hardness tester) is usually about 1 to 20 kg, preferably about 2 to 15 kg, more preferably 3 to 8 kg.

In the above-mentioned fine granules, "fine granules having an average particle diameter of 400 pzn or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt" are novel.

The "fine granules" have an average particle diameter of about 400 μm or less, preferably 350 μm or less. Preferably; the average particle diameter of the fine granules is 300 to 400 μm. Aside from the average particle diameter of the "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 400 μm or less.

Regarding the fine granule of the present invention, the dissolution of the physiologically active substance can be controlled by formulating the coat (coating layer) to have different viscosity or content of the water-soluble polymer (e.g., HPC, HPMC and so forth) or by formulating the coat to have a controlled ratio of the ethanol-soluble water-soluble polymer (e.g., HPC) and the ethanol-insoluble water-soluble polymer (e.g., HPMC). The dissolution of the physiologically active substance is not very influenced by liquidity, which can be suitably controlled.

As a pharmaceutical preparation which comprises the "fine granules" of the present invention, there may be employed, for example a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc; a liquid preparation such as suspension preparation, etc. Among others, preferred is a tablet, more preferred is an orally disintegrable tablet.

When the "fine granule" of the present invention is used for a tablet except for an orally disintegrable tablet, the diameter of the tablet is about 5 to 10 mm, preferably about 5 to 8 mm. When the fine granule of the present invention is used for a capsule, the size of the capsule is preferably a #2 capsule or less.

The "orally disintegrable tablet" of the present invention is and the "pharmaceutical preparation which comprises the fine granules of the present invention" may contain a foaming component to impart a refreshing feeling at administration. Also, with an effervescent comprising the foaming component, the dissolution can be precisely controlled compared to the case of a fine granule alone. As the foaming component, various compounds can be employed as long as safety is not interfered with. Examples of the foaming component include alkaline metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.) and ammonium carbonate and so forth. The foaming component(s) may be employed alone or in an admixture of two or more thereof. The preferable foaming component includes sodium carbonate, sodium hydrogencarbonate, ammonium carbonate and so forth. The ratio of the foaming component can be selected within the range in which it is possible to impart the foam, for example, about 10 to 2500 weight %, preferably about 50 to 2000 weight % (e.g., about 75 to 1500 weight %), more preferably about 100 to 1000 weight %, relative to 100 weight % of the fine granule.

In employing the effervescent and the fine granule having small particle diameter, it is advantageous to quickly prepare a homogeneous aqueous solution or suspension, and to maintain the dispersed condition. But, in case that the particle diameter is too small, the problem tends to occur that the fine granule adheres to the wall of a machine by static electricity during production processes.

The specific volume of the above fine granule is about 3 ml/g or less, preferably about 2 ml/g or less. In order to maintain the homogeneous condition of the fine granule in the suspension obtained by adding the foaming agent composition, the specific volume can be suitably selected in the above range according to the specific gravity (specific volume) of the dispersion medium.

The "composition" in the present invention can be produced by a known granulation method.

The "granulation method" includes, for example, rolling granulation method (e.g., centrifugal rolling granulation, etc.), fluidized-bed granulation (e.g., rolling fluidized bed granulation, fluidized granulation, etc.), stirring granulation and so forth. Among others, preferred is fluidized-bed granulation method, more preferred is rolling fluidized-bed granulation method.

Concrete example of the "rolling granulation method" includes a method using "CF apparatus" manufactured by Freund Industrial Co., Ltd. (Japan) and so forth. Concrete examples of the "rolling fluidized-bed granulation method" include methods using "SPIR-A-FLOW", "multi plex" manufactured by Powrex Corp. (U.S.A.), "New-Marumerizer" manufactured by Fuji Paudal Co., Ltd. (Japan), and so forth. The method for spraying the mixture can be suitably selected in accordance with the kind of granulator, and may be, for example, any one of a top spray method, a bottom spray method, a tangential spray method, and so forth. Among others, a tangential spray method is preferred.

The "composition" in the present invention. can be produced in accordance with, for example, a method which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance.

For example, employed is a method described in JP-A-5-92918 (coating method), which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance, if necessary together with a basic inorganic salt, binders, lubricants, excipients, a water-soluble polymer, etc. (hereinafter, may be abbreviated to "coating layer"). For example, employed is a method which comprises coating a core with an acid-labile physiologically active substance and a basic inorganic salt, and then further with binders, lubricants, excipients, a water-soluble polymer, etc.

The average particle diameter of the "cores" is about 250 μm or less, preferably about 50 to 250 μm, more preferably about 100 to 250 μm, especially preferably about 100 to 200 μm. The "cores" having the above average particle diameter include particles which all pass through a #50 sieve (300 μm), particles where about 5 w/w % or less of the total remain on a #60 sieve (250 μm), and particles where about 10 w/w % or less of the total pass through a #282 sieve (53 μm) The specific volume of the "core" is about 5 ml/g or less, preferably about 3 ml/g or less.

Examples of the "core" include

(1) a spherical granulated product comprising crystalline cellulose and lactose, (2) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (avicel SP, manufactured by Asahi Chemical Co., Ltd. (Japan)), (3) a stirring granulated product being about 50 to 250 μm and comprising lactose (9 parts) and a starch (1 part), (4) a micro particle being about 250 μm or less classified as a spherical granule comprising micro crystalline cellulose described in JP-A-61-213201, (5) a processed product such as wax formed to a sphere by spraying or melting granulation, (6) a processed product such as gelatin beads comprising oil component, (7) calcium silicate, (8) starch, (9) a porous particle such as chitin, cellulose, chitosan, etc, and (10) a bulk product such as granulated sugar, crystalline lactose or sodium chloride, and processed preparations thereof. Further, these cores may be produced in accordance with per se known grinding method or granulation method, and sifted to prepare the particles having the desired particle diameter.

The above "spherical granulated product comprising crystalline cellulose and lactose" includes, for example (i) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (ii) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil NP-7:3, manufactured by Freund Industrial Co., Ltd. (Japan)], (iii) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts) [e.g., Nonpareil 105T (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (iv) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (5 parts) and lactose (5 parts) [e.g., Nonpareil NP-5:5, manufactured by Freund Industrial Co., Ltd. (Japan)], and so forth.

In order to produce a pharmaceutical preparation which is superior in dissolution while retaining suitable strength, the "core" includes, for example, preferably the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated material comprising crystalline cellulose and lactose and containing 50 weight % or more of lactose. Among others, preferred in a core comprising 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

As the "core" employed in the present invention, in particular, there may be employed the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated product with a diameter of about 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts).

The "core" may contain the physiologically active substance such as the above described pharmaceutical ingredient. Also, the "core" may not contain the physiologically active substance because the release of the physiologically active substance can be controlled by a coating layer containing the physiologically active substance.

The "core" is preferably as uniform a sphere as possible, for reducing the irregularity of the coating, in addition to being a powdery core.

The ratio of the "coating layer" to the "core" can be selected within the range in which it is possible to control dissolution of the physiologically active substance and particle size of the composition, for example, usually about 50 to 400 weight % relative to 100 weight % of the core.

The coating layer may be constructed by plural layers. At least one layer of the plural layers must contain the physiologically active substance. The combination of various layers such as a coating layer not containing the active ingredient, a base coating layer, and an enteric coating layer which constitute the coating layer can be suitably selected.

In case that the "core" is coated, for example, the above physiologically active substance and the water-soluble polymer can be employed in admixture thereof. The admixture may be a solution or a dispersion, and can be prepared by using an organic solvent such as water or ethanol or an admixture thereof.

The concentration of the water-soluble polymer in the admixture varies according to the ratio of the physiologically active substance and the excipients, and is usually about 0.1 to 50 weight %, preferably about 0.5 to 10 weight %, in order to retain the binding strength of the physiologically active substance to the core and maintain the viscosity of the mixture so as not to reduce the workability.

Where the coating layer comprises plural layers, the concentration of the physiologically active substance in each layer may be changed successively or gradually by selecting for the content ratio or viscosity of the water-soluble polymer or by successive coating with mixtures varying in the ratio of the physiologically active substance and the other excipients. In the above case, it may be coated with a mixture in which the content ratio of the water-soluble polymer is out of the range of about 0.1 to 50 weight %, as long as the coating layer as a whole contains about 0.1 to 50 weight % of the water-soluble polymer. Further, in forming the inactive coat according to known methods, the coating layer may comprise some layers such that the inactive layer may block each layer containing the physiologically active substance.

Also, in case of two or more physiologically active substances not suited in the compatibility, the core may be coated by employing each mixture together or separately.

The above coated material is dried, and passed through sieves to obtain a "composition" having uniform size. Because the form of the powder is usually according to the core, a fine granule being in the form of a rough sphere may be obtained. As the sieve may be employed, for example a #50 circular sieve (3001 μm). The composition is obtained by selecting those which pass through the #50 circular sieve.

The "fine granule" in the present invention can be produced in accordance with in the same manner as above granulation method, for example, a method which comprises coating the composition with an enteric coating layer, in order to protect the acid-labile physiologically active substance or to impart enteric dissolution. If necessary, the composition coated with an enteric coating layer may be further coated by a water-soluble sugar alcohol, preferably mannitol. In such case, the strength of the orally disintegrable tablet comprising fine granules is improved.

The "enteric coating layer" is preferably a layer having about 20 to 70 μm, preferably about 30 to 50 μm of thickness and coating the whole surface of the composition containing the physiologically active substance. Accordingly, the smaller particle diameter of the composition, the higher the weight % of the enteric coating layer in the whole fine granule. In the fine granule of the present invention, the "enteric coating layer" is about 30 to 70 weight %, preferably about 50 to 70 weight %, of the fine granule as a whole.

The "enteric coating layer" may be constructed by plural (e.g., 2 or 3) layers. For example, employed is a method which comprises coating a composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, followed by being coated with an enteric coating layer having polyethyleneglycol.

The "orally disintegrable tablet" of the present invention can be produced in accordance with a conventional method in the pharmaceutical field. Such methods include, for instance, a method which comprises blending the "fine granules" and the "additives", and molding, if necessary followed by drying. Concretely mentioned is a method which comprises blending the fine granules and the additives, if necessary with water, and molding, if necessary followed by drying.

The "blending procedure" can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc. The above "blending procedure" is carried out, for instance, by using an apparatus such as Vertical Granulator GV10 [manufactured by Powrex Corp. (Japan)], Universal Kneader [manufactured by Hata Iron Works Co., Ltd. (Japan)], fluidized bed granulator LAB-1 and FD-3S [manufactured by Powrex Corp. (Japan)], V-shape mixer, tumbling mixer, and so forth.

Preferred example of the method for the "orally disintegrable tablet" of the present invention is a method which comprises:

(i) coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance and a basic inorganic salt, followed by being coated with a coating layer comprising a water-soluble polymer to obtain a composition,

(ii) coating the resultant composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, and then with an enteric coating layer having polyethyleneglycol, followed by being coated by mannitol to obtain fine granule, and

(iii) blending the resultant fine granule with an additive, followed by molding.

Where the pharmaceutical preparation of the present invention, especially an orally disintegrable tablet, is one which comprises no lubricant inside the preparation or tablet, such preparation can be preferably produced in accordance with methods described in JP-A-56-14098, Japanese Patent No. 2681601, etc. Such preparation, especially an orally disintegrable tablet, has sufficient strength. The above lubricant includes, for example, magnesium stearate, sucrose fattyacid ester, polyethyleneglycol, talc, stearic acid, etc.

The pharmaceutical preparations such as solid preparation (e.g., tablets, granules, fine granules, capsules, effervescents, etc.) and liquid preparation such as suspending preparation, which comprises the "fine granules" of the present invention can be produced in accordance with a conventional method.

The solid pharmaceutical preparation containing the "fine granules" of the present invention and the "orally disintegrable tablet" of the invention can also be produced by the wet tabletting method. As the above method, it is preferably employed the methods described in JP-A-5-271054 and so forth. They can also be produced by drying after humidification. As the above method, preferably employed are the methods described in JP-A-9-48726, JP-A-8-291051 and so forth. Namely, it is effective to humidify before tabletting or after tabletting and then to dry, in order to enhance the hardness.

The "molding procedure" can be carried out, for instance, by tabletting with a pressure of 0.5 to 3 ton/cm^2, preferably 1 to 2 ton/cm^2 by using a single-punch tabletting machine [Kikusui Seisakusho (Japan)] or a rotary type tabletting machine [Kikusui Seisakusho (Japan)] when a solid preparation is a tablet, especially an orally disintegrable tablet.

The "drying procedure" can be carried out by any of the techniques used commonly in the art, such as vacuum drying, fluidized-bed drying, etc.

The "fine granules" of the invention can be used for a pharmaceutical preparation. The pharmaceutical preparation includes, for example, a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc.; a liquid preparation such as a suspension preparation, etc. Among others, a tablet is preferred. Such tablet preferably has suitable strength so as to be stable through production processes and distributions.

A solid pharmaceutical preparation comprising the fine granule of the invention is used for an orally disintegrable tablet and can be administered without water or together with water.

As administration methods, there are listed (1) a method of administration by dissolution or disintegration together with a little water, or without water and with saliva in the oral cavity, not to be swallowed as it is, or (2) a method of administration with water, where it is swallowed as it is. Also, the tablet may be administered dissolved or disintegrated with water.

The "orally disintegrable tablet" of the present invention is advantageously used in (a) cases where administration without water is necessary, (b) cases of administration to a patients who have difficulty in swallowing tablets, or (c) cases of administration to the aged or to children where there is a fear of blocking the throat if it is in usual tablet form.

In case of the above (a), the orally disintegrable tablet is preferably used for antipyretic agents, analgesic agents, anti-inflammatory agents, antianxiety drugs, antitussive-expectorants, anti motion sickness agents, drugs for prevention and treatment for car-sickness, and so forth.

In case of the above (b), the orally disintegrable tablet is preferably used for preventing and/or treating hypertension, hyperlipemia, diabetes, bronchial asthma, cerebrovascular diseases, and so forth.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be safely administered orally to mammals such as mice, rats, rabbits, cats, dogs, bovines, horses, monkeys, humans, etc.

With the dosage of the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention, varies depending on the pharmaceutically active ingredient, subject, kinds of diseases, etc., the dosage can be selected so that the dosage of the pharmaceutically active ingredient is an effective amount.

For instance, when a benzimidazole compound (I) or a salt thereof such as lansoprazole is employed as an acid-labile physiologically active substance, especially a pharmaceutically active ingredient, the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention is useful for treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, anastomotic ulcer, Zollinger-Ellison syndrome, etc), gastritis, reflux esophagitis, etc.; eradication of *H. pylori;* suppression of gastrointestinal bleeding caused by digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of gastrointestinal bleeding caused by invasive stress (e.g., stress caused by cerebrovascular disease, head injury, failure of many organs, burn injury of a wide range, which necessitate a large-scale operation necessitating the following intensive management, or intensive care); treatment and prevention of ulcer caused by non-steroidal anti-inflammatory agent; treatment and prevention of gastric hyperacidity and ulcer caused by postoperative stress; administration before anesthesia, etc. The dosage of the preparation per an adult (body weight: 60 kg) is about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, as a benzimidazole compound (I) or a salt thereof such as lansoprazole.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be administered once a day, or two or three times separately a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples and Reference Examples are further illustrative but by no means limitative of the present invention.

Unless otherwise specifically indicated, the following "%" means weight %.

Also, the content of the hydroxypropoxyl group is measured in accordance with the methods described in Japanese Pharmacopoeia (13th edition).

The physical properties of the tablets and granules prepared in Examples were determined by the following test methods.

(1) Hardness Test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo, Co. Ltd. (Japan)]. The test was performed in 10 runs and mean values were shown.

(2) Oral Disintegration Time

Time for complete disintegration only by saliva in the oral cavity was determined.

(3) Remaining Ratio

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml of 0.1N HCl (75 rpm) for 1 hour. Then, the enteric fine granule was collected by means of the sieve. The content of the drug in the collected fine granule was measured by the HPLC method. The remaining ratio was calculated according to the following expression with the content of the drug in the tablet which is measured separately by HPLC method.

Remaining ratio=(Content of the drug in the collected fine granule after the dissolution test using 0.1N HCl for 1 hour)/(Content of the drug in the tablet)

(4) Acid-resistance: Dissolution using 0.1N HCl

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml f 0.1N HCl (75 rpm) for hour. Then, test medium was collected and filtered by using a 0.45 μm membrane filter. The absorbance way measured to calculate the dissolution of the drug into 0.1N HCl.

(5) Average Particle Diameter: Volume Based Distribution Median Diameter (median diameter: 50% Particle Diameter from Cumulative Distribution)

Determination was carried out with Raser Diffraction Analyzer, type; HEROS RODOS [trade name, manufactured by Sympatec (Germany)].

EXAMPLES

Example 1

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil is coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation is stopped when the specified amount of the bulk liquid has been sprayed, and then drying is carried out in the granulator for 7 minutes. The resulting granules are sieved through a #60 circular sieve (250 Am) and a #100 circular sieve (150 μm) to provide 750 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70°0 C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 650 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 17 g/min. The coated powders are dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	23.1 g
Talc	16.0 g
Polysorbate 80	9.0 g
Yellow iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] is charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8 %, manufactured by Shin-Etsu Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation is carried out while spraying a solution which is prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules are dried to provide granulated powders. To the granulated powders are added 90.0 g of crospovidone and 5.4 g of magnesium stearate, which is admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

Hereinafter, the above "enteric coated granules having a core" is referred to as "enteric coated powders".

200.0 g of the above enteric coated powders and 300.0 g of the above mixed powders are tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 500 mg.

Reference Example 1

An alkaline cellulose comprising 24.1% of NaOH, 1.7% of Na_2CO_3, 42.9% of cellulose, 31.8% of H_2O was obtained by immersing a wood pulp in 49% aqueous solution of sodium hydroxide and then by pressing it. A reactor was charged with 100 weight parts of the alkaline cellulose. Then, nitrogen gas replacement was carried out. After the replacement, 5 weight parts of propylene oxide was charged in the reactor and reacted with stirring at 40° C. for 1 hour, at 50° C. for 1 hour and at 70° C. for 1 hour to obtain 103 weight parts of a reactant.

On the other side, a kneader was charged with 2.5 weight parts of hot water at 65° C. and 0.13 weight parts of glacial acetic acid (about 40 weight % against equivalent for neutralization, initial neutralized acid) and therein, 1 weight part of the above resulting alkaline cellulose was dispersed. Then, the temperature was set at 30° C. to dissolve a part of the reactant, and 0.20 weight part of glacial acetic acid (the remainder of an equivalent for neutralization, complete neutralized acid) to obtain a processed fiber product containing a part of dissolution and a part of deposit.

The resulting product was washed with hot water at about 80° C., drained, dried, ground by means of a high rolling impact grinder, and sifted by means of a 100 mesh sieve to obtain the powder of low-substituted hydroxypropyl cellulose LH-33 (the content of hydroxypropoxyl group: 5.8 weight %, the average particle diameter: 17.8 μm).

Reference Example 2

Powders of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.7 weight %, average particle diameter: 30.8 μm) were obtained in the same manner as in Reference Example 1.

Example 2

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 [(trade name) particle diameter: 100 to 200 μm]. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 30° C., respectively, the Nonpareil was coated by spraying a spray liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min., and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2186 g of powders (150 to 300 μm) having a core.

Spray Liquid:

Lansoprazole	927 g
Magnesium carbonate	309 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 wt %) (average particle diameter: 17.57 μm)	154.5 g
Hydroxypropyl cellulose (Type SSL)	309 g
Purified water	3955 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2040 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an

undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. to provide 2145 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	264 g
Purified water	5016 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1710 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 17 g/min., and dried for 7 minutes, and then sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 2393 g of enteric coated powders (177 to 355 μm) having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	5016.4 g
Eudragit NE30D	559.0 g
Triethyl citrate	333.7 g
Glyceryl monostearate	106.5 g
Polysorbate 80	34.8 g
Red iron oxide	1.8 g
Purified water	2547.1 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 600 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 32° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 11 g/min., and then dried for 7 minutes to provide 617 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 334.1 μm.

Film Coating Liquid:

Mannitol	33 g
Purified water	297 g

(5) Production of Mannitol-granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] was charged with 800 g of mannitol [manufactured by Merck Japan Co., Ltd.], and granulation was carried out while spraying 315 g of purified water. The granules were dried to provide 727.3 g of granulated powders.

(6) Production of Mixed Powders

To 97.3 g of the above mannitol-granulated powders were added 105 g of the above enteric coated and mannitol coated granules having a core, 15.0 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 22.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 7.5 g of crospovidone, 1.5 g of citric acid anhydrous, 0.45 g of aspartame and 0.75 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(7) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 5.9 kg and 30 seconds, respectively.

Example 3

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 29° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #60 circular sieve (250 μm) and a #100 circular sieve (150 μm) to provide 2424 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)) was charged with 2337.5 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 6050 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 2551 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropyl methylcellulose (Type 2910, viscosity: 3 centistokes)	332.5 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %) (average particle diameter: 17.57 μm)	17.5 g
Purified water	6650 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 570 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 2646 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The coated powders were sieved through a #42 circular sieve (355 μm) and a #70 circular sieve (212 μm) to provide 1116 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 326.9 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1911 g
Eudragit NE30D	212.9 g
Triethyl citrate	127.1 g
Glyceryl monostearate	40.6 g
Polysorbate 80	13.3 g
Red iron oxide	0.8 g
Purified water	970.3 g

(4) Production of Mixed Powders

To 200 g of the above enteric coated granules having a core were added 189.7 g of mannitol, 30.0 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 60.0 g of crystalline cellulose RCEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15.0 g of crospovidone, 2.8 g of citric acid anhydrous and 25 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 4.2 kg and 24 seconds, respectively.

Example 4

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (TyDp 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 32° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2280 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1020 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 15 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1330.5 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	120 g
Titanium oxide (TiO_2)	240 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	240 g
Magnesium carbonate	120 g
Purified water	2880 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan)], MP-10 (Type 2)1 was charged with 460 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. The spraying operation was stopped when the specified amount 2205 of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid:

Eudragit L30D-55	2290 g
Eudragit NE30D	253 g
Triethyl citrate	153 g
Glyceryl monostearate	20 g
Polysorbate 80	8 g
Titanium oxide (TiO_2)	53 g
Sterilized Talc H (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	53 g
Purified water	2420 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 16 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex dorD. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 824 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minute. The resulting granules were sieved through a #42 circular sieve (355 μm) and a #60 circular sieve (250 μm) to provide 806 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 326.6 μm.

Film Coating Liquid:

Mannitol	320 g
Purified water	2880 g

(5) Production of Mixed Powders

To 120 g of the above enteric coated and mannitol coated granules having a core were added 87.75 g of mannitol, 8.5 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %), 4.5 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 19.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 6.5 g of crospovidone, 1.3 g of citric acid anhydrous, 1.3 g of aspartame and 0.65 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.9 kg and 20.5 seconds, respectively.

The remaining ratio of the obtained tablet after acid-resistance test was 97%.

Example 5

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 1.05 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the Specified amount 5661 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2074 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2555 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1320 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance With the tangential spray method at a spray rate of 22 g/min. The specified amount 1638 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1219.2 g
Eudragit NE30D	134.4 g
Polyethylene glycol 6000	40.8 g
Glyceryl monostearate	24.0 g
Polysorbate 80	7.2 g
Ferric oxide	0.24 g
Ferric oxide (yellow)	0.24 g
Citric acid anhydrous	0.48 g
Purified water	1693 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 42° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 6552 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g

-continued

Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 35° C., respectively an f film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1964 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 333.7 μm.

Film coating liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/Cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 2.6 kg and 20 seconds, respectively.

The acid-resistance of the obtained tablet was 3.5%.

Example 6

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 4717. 5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1811 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1811 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray imethod at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5274 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2628 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1560 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 6048 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g

-continued

Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 72° C. and about 42° C, respectively, an enteric film coating liquid (B) of the following composition preepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	609.6 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	846.7 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 38° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 17 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2825 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 330.5 μm.

Film Coating Liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KC-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 2 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.1 kg and 22 seconds, respectively.

The acid-resistance of the obtained tablet was 2.5%.

Example 7

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 4717.5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1842 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fliudized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1842 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 74° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared an advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The spraying operation was stopped when the specified amount 5365 g of the undercoatingliquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a#42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2770 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1300 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 39° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5040 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 16 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2453 g of enteric coated granules having a core.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1000 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 38° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 273 g of the enteric film coating liquid had, been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	610.4 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	845.12 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 20 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 294 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1061 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 307.1 μm.

Film Coating Liquid:

Mannitol	120 g
Purified water	720 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 207 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.2 kg and 24 seconds, respectively.

Example 8

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105T (trade name) (particle diameter of 100 to 200 m). With the inlet air temperature and the temperature of the loading being controlled at 71 to 78° C. and about 31° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5550 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 21 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1723 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluided coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 77° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 2787 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 13 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1958 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized Goating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1100 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 1365 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1017.3 g
Eudragit NE30D	113.3 g
Polyethylene glycol 6000	34.0 g
Glyceryl monostearate	20.0 g
Polysorbate 80	6.0 g
Ferric oxide	0.2 g
Ferric oxide (yellow)	0.2 g
Citric acid anhydrous	0.4 g
Purified water	1410.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 41° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 5040 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	3360 g
Eudragit NE30D	373.2 g
Triethyl citrate	224.4 g
Glyceryl monostearate	72.0 g
Polysorbate 80	21.6 g
Ferric oxide	0.72 g
Ferric oxide (yellow)	0.72 g
Citric acid anhydrous	0.6 g
Purified water	1706.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The specified amount 682.5 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 36° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 735 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2319.5 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules; was 392.7 μm.

Film Coating Liquid:

Mannitol	100 g
Purified water	600 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hyaroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of [crospovidone, 3 g of citric acid anhyaroug, 9 g of dspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 12 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.7 kg and 35 seconds, respectively.

The acid-resistance of the obtained tablet was 3.4%.

Example 9

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator (manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 7 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 757 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g

-continued

HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 672 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a sprayer rate of 17 g/min. The Coated powders were dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 285.4 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	16.5 g
Talc	16.0 g
Polysorbate 80	9.0 g
Iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp., (Japan), LAB-1] was charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8%, manufactured by Shin-PteU Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation was carried out while spraying a solution which was prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules were dried to provide granulated powders. To the granulated powders were added 90.0 g of crospovidone and 5.4 a of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

200.0 g of the above enteric coated granules having a core and 300.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness, the oral disintegration time and remaining ratio after acid-resistance test of each tablet thus obtained were 4.2 kg, 27 seconds and 96.3%, respectively.

INDUSTRIAL APPLICABILITY

The orally disintegrable tablet of the present invention has superior disintegrability or dissolution so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged of children and easily administered without water. Also, because the orally disintegrable tablet of the present invention contains fine granules having the average particle diameter and an enteric coating layer such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration and has superior acid-resistance.

Further, because the orally disintegrable tablet of the present invention has a suitable strength such that it will not be substantially damaged through production processes or circulation processes, it is superior in stability for long-term storage and easy of use at the administration.

Further, because the fine granule of the present invention is characterized in that it stably retains the acid-labile physiologically active substance, contains the physiologically active substance in high content, be small and has superior stability, it can be used for producing various compact pharmaceutical preparations such as tablets, capsules, suspensions and so forth. Such preparations are easy of use at the administration. In addition, the fine granule of the present invention has superior acid-resistance after compression.

What is claimed is:

1. An orally disintegrable tablet which comprises

(i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having 10 weight % or more of an acid-labile physiologically active substrate that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to about 20 kg, is orally disintegrable.

2. An orally disintegrable tablet of claim 1, wherein the average particle diameter of the fine granule is 300 to 400 μm.

3. An orally disintegrable tablet of claim 1, wherein the fine granules further comprise a basic inorganic salt.

4. An orally disintegrable tablet of claim 1, wherein the additive comprises a water-soluble sugar alcohol.

5. An orally disintegrable tablet of claim 1, wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol.

6. An orally disintegrable tablet of claim 4, wherein the additive comprises (1) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose.

7. An orally disintegrable tablet of claim 1, wherein the particle diameter of the fine granules is practically 425 μm or less.

8. An orally disintegrable tablet of claim 1, wherein the particle diameter of the fine granules is practically 400 μm or less.

9. An orally disintegrable tablet of claim 3, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

10. An orally disintegrable tablet of claim 1, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

11. An orally disintegrable tablet of claim 10, wherein the core comprises 50 weight % or more of lactose.

12. An orally disintegrable tablet of claim 10, wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

13. An orally disintegrable tablet of claim 1, wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance.

14. An orally disintegrable tablet of claim 1, wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance.

15. An orally disintegrable tablet of claim 1, wherein the fine granules are produced by fluidized-bed granulation method.

16. An orally disintegrable tablet of claim 1, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

17. An orally disintegrable tablet of claim 16, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

18. An orally disintegrable tablet of claim 1, wherein the sustained-release agent is a methacrylate copolymer.

19. An orally disintegrable tablet of claim 16, wherein the sustained-release agent is in an amount of 5 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

20. An orally disintegrable tablet of claim 4, wherein the water-soluble sugar alcohol is erythritol.

21. An orally disintegrable tablet of claim 4, wherein the water-soluble sugar alcohol si mannitol.

22. An orally disintegrable tablet of claim 5, wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

23. An orally disintegrable tablet of claim 4, wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule.

24. An orally disentegrable tablet of claim 6, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %.

25. An orally disintegrable tablet of claim 6, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropoxyl cellulose is 5.0 7.0 weight %.

26. An orally disintegrable tablet of claim 1, which further comprises crosprovidone.

27. An orally disintegrable tablet of claim 1, wherein the oral disintegration time is one minute or less.

28. An orally disintegrable tablet of claim 1, which comprises no lubricant inside the tablet.

29. Fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having (i) 25

weight % or more of an acid-liable physiologically active substance that is lansoprazole and (ii) a basic inorganic salt.

30. Fine granules of claim **28**, wherein the average particle diameter of the fine granules is 300 to 400 μm.

31. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 425 μm or less.

32. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 400 μm or less.

33. Fine granules of claim **28**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

34. Fine granules of claim **28**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

35. Fine granules of claim **34**, wherein the core comprises 50 weight % or more of lactose.

36. Fine granules of claim **28**, wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance.

37. Fine granules of claim **28**, which are produced by fluidized-bed granulation method.

38. Fine granules of claim **28**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

39. Fine granules of claim **38**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

40. Fine granules of claim **28**, wherien the sustained-release agent is a methacrylate copolymer.

41. Fine granules of claim **28**, wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

42. Fine granules of claim **28**, wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules.

43. A tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of claim **28**.

44. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 to 30 weight % relative to 100 weight % of the aqueous enteric polymer agent.

45. Fine granules of claim **38**, wherein the sustained-release agent is in an amount of 5 to 30% relative to 100 weight % of the aqueous enteric polymer agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,328,994 B1 Page 1 of 1
DATED : December 11, 2001
INVENTOR(S) : Toshihiro Shimizu, Shuji Morimoto and Tetsuo Tabata

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 37,
Line 8, the word "substrate" should read -- substance --

Column 38,
Line 2, the word "si" should read -- is --

Signed and Sealed this

Fifth Day of August, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,328,994 B1
APPLICATION NO. : 09/355781
DATED : December 11, 2001
INVENTOR(S) : Shimizu et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

First page, first column, line 4 of Foreign Application Priority Data: This line should be deleted in its entirety.
Column 37, line 50(claim 1): “substrate” should read --substance--.
Column 37, line 66(claim 6): “(1)” should read --(i)--.
Column 38, line 36(claim 19): “of 5 15 weight %” should read --of 5 to 15 weight %--.
Column 38, line 42(claim 21): “si” should read --is--.
Column 38, line 47(claim 23): “claim 4” should read --claim 6--.
Column 38, line 56(claim 25): “5.0 7.0 weight %” should read --5.0 to 7.0 weight %--.
Column 39, line 3(claim 30): “claim 28” should read --claim 29--.
Column 39, line 5(claim 31): “claim 28” should read --claim 29--.
Column 39, line 7(claim 32): “claim 28” should read --claim 29--.
Column 39, line 9(claim 33): “claim 28” should read --claim 29--.
Column 39, line 11(claim 34): “claim 28” should read --claim 29--.
Column 39, line 17(claim 36): “claim 28” should read --claim 29--.
Column 39, line 20(claim 37): “claim 28” should read --claim 29--.
Column 39, line 22(claim 38): “claim 28” should read --claim 29--.
Column 40, line 3(claim 40): “claim 28” should read --claim 29--.
Column 40, line 5(claim 41): “claim 28” should read --claim 38--.
Column 40, line 8(claim 42): “claim 28” should read --claim 29--.
Column 40, line 13(claim 43): “claim 28” should read --claim 29--.

Signed and Sealed this

Tenth Day of July, 2007

JON W. DUDAS
Director of the United States Patent and Trademark Office

CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of September 2016, I caused a copy of the foregoing Corrected Opening Brief for Appellants to be served by electronic means via the Court's CM/ECF system on all counsel registered to receive electronic notices.

/s/ Arlene L. Chow

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 7,814 words.

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the typestyle requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Office Word in Times New Roman 14-point font.

/s/ Arlene L. Chow